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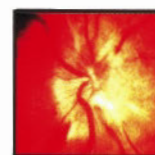
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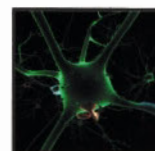
**INTERNAL MEDICINE REVIEW
CORE CURRICULUM**

BOOK **5**

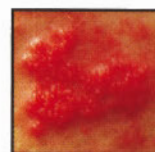
GENERAL INTERNAL MEDICINE



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DERMATOLOGY



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Figure 3-1. *Medianium System*

Review of Pleurovac components (Figure 3-1).

3 chambers:

- 1) First chamber (nearest the patient) = **Collection chamber** - where whatever effluent from the pleural cavity is collected.
- 2) Second chamber (middle) = **Water-seal chamber** - allows air to bubble out from the chest. Bubbles in this chamber indicate air is in (or still entering) the pleural space.
- 3) Third chamber (attached to suction) = **Suction regulator** - the height of water determines the amount of suction applied to the chest tube (when vacuum is applied to the chamber and there is bubbling in the water of the chest tube with $< 90\%$ expansion of lung).

* If there is a leak with $> 90\%$ expansion of lung, thoracic surgery (VATS) or thoracostomy or intubate.

* If there is no expansion, suggests a bronchopleural fistula or surgical intervention.

INTERNAL MEDICINE REVIEW

CORE CURRICULUM

15th EDITION

Book 5 of 5

Topics in this volume:

General Internal Medicine

Neurology

Dermatology

Robert A. Hannaman, MD
with Candace L. Walkley, MD and J. Thomas Cross, Jr., MD, MPH, FACP

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I N T E R N A L M E D I C I N E R E V I E W



CORE CURRICULUM

15th EDITION

Robert A. Hannaman, MD
with J. Thomas Cross, Jr., MD, MPH, FACP

GENERAL INTERNAL MEDICINE

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General Internal Medicine

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PHARMACOLOGY

PHARMACOKINETICS

Absorption

First-pass effect: Oral drugs are absorbed from the GI tract, pass through the portal vein, and then enter the liver. Drugs metabolized by the liver will then undergo “first-pass” metabolism. These drugs require a much higher oral dose to be as effective as a parenteral dose of the same medicine because of this first-pass metabolism. Common drugs that undergo first-pass effect:

- Opiate-related: meperidine, morphine, and naloxone
- Calcium antagonists: nifedipine, verapamil, and diltiazem
- Some beta-blockers: labetalol, metoprolol, and propranolol
- Tricyclic antidepressants
- Benzodiazepines (BDZs)
- Anticonvulsants: valproic acid and phenytoin
- NSAIDs: ibuprofen, ketoprofen, naproxen, and indomethacin
- Other: cyclophosphamide, theophylline, warfarin, and metronidazole

Some drugs require an acidic environment for absorption—especially the **azole antifungals** (except fluconazole and voriconazole) and **thyroid** hormone. These drugs should **not** be used with H_2 blockers or proton pump inhibitors (PPIs). PPIs can also block calcium absorption.

A very important interaction that interferes with absorption occurs when cations (e.g., calcium and iron supplements or antacids containing magnesium and aluminum) combine with thyroid hormone or quinolones.

Distribution

Volume of distribution (V) [Know]: This is the effective volume for determining the total amount of drug in the body **and** for determining the loading dose. The total amount of drug in the body (D_T) is equal to the volume $\times$ concentration:

$$D_T = V (C_p)$$

So the volume of distribution is:

$$V = D_T / C_p$$

V = the volume of distribution. This is the **apparent** volume into which the drug is dispersed. C_p is the concentration of the drug in the plasma. If the tissues hold more drug than the plasma at equilibrium, “V” will be large. Rule of thumb: If the drug is dosed at each half-life, the total amount of drug (D_T) is **double** the maintenance dose.

Note that the loading dose does **not** depend on excretion capability! The loading dose in a patient with renal failure is the **same** as that in a healthy patient; **but** if the drug is cleared by the kidney, the subsequent maintenance dose will be very different.

Excretion

Drugs excreted mainly by the **liver** include all of those mentioned above under first-pass effect.

In a person with cirrhosis, the decreased first-pass effect increases the effective bioavailability of the above drugs. Clearance is also decreased, so the effective dose of a drug may be very small.

Meperidine is metabolized by the liver to normeperidine, which is an active metabolite causing CNS stimulation (including seizures); therefore, in liver disease, there is less first-pass effect. Normeperidine is cleared by the kidney. So, carefully watch a patient with hepatic **or** renal dysfunction when on meperidine!

First-Order Kinetics

First-order kinetics: The rate at which a drug is cleared is **independent** of the drug concentration. After one half-life, the drug level in the body will be only half of the initial level. It is possible to determine the half-life by checking 2 blood levels at a certain interval (between doses).

As seen in **Table 10-1**, 5 half-lives after a patient is started on a first-order drug **without** a loading dose, the drug level will be 97% of steady state. Also, if a first-order drug is stopped, the drug will be 97% gone after 5 half-lives. So, when starting patients on a medication with no loading dose, usually wait 3–5 half-lives before rechecking the blood level to see if you need to adjust the dosage.

Michaelis-Menton or Saturable Pharmacokinetics

These clearance processes are non-linear and occur when a metabolizing enzyme system is saturated. Steady-state drug serum concentrations increase in disproportion to dose changes. Because clearance is

Table 10-1: Half-Lives

# of Half-lives	Percent of Steady State
1	50
2	75
3	87.5
4	93.75
5	96.875

dose- or concentration-dependent, half-life changes as the concentration/dose of the drug changes. Because steady-state serum concentration is often well below the saturability of enzyme systems, linear pharmacokinetics are the norm for most medications. Zero-order pharmacokinetics is another name for Michaelis-Menton pharmacokinetics. While most medications are metabolized in linear fashion, in overdoses they may assume zero-order pharmacokinetics because the drug concentration far exceeds the therapeutic range.

Drug Interactions

Note

There are thousands of drug interactions, but several are very serious—and thus frequently on the Boards. We will cover some of the most serious ones here.

Warfarin Interactions

Table 10-2 outlines the most important warfarin interactions that result in increased INR (international normalized ratio). Especially know that trimethoprim/sulfamethoxazole (TMP/SMX) can markedly raise the INR within the first few days of therapy. TMP/SMX both displaces warfarin from protein-binding sites and decreases warfarin metabolism. However, any antibiotic can affect the INR without affecting warfarin metabolism by decreasing vitamin-producing bacteria in the intestine.

Two studies have shown increased INR with warfarin + acetaminophen: > 9,100 mg/week led to 10x risk of having INR > 6.

Natural products with the potential to enhance the anti-coagulant effect of warfarin include glucosamine, ginkgo, garlic, feverfew, and dong quai.

Drugs that Cause Hyperkalemia

ACE (angiotensin converting enzyme) inhibitors, ARBs, (angiotensin receptor blockers), spironolactone and other potassium-sparing diuretics, and heparin can cause severe hyperkalemia. The risk is far greater when several of these drugs are combined (as seen in the treatment of heart failure). Trimethoprim can cause hyperkalemia by blocking amiloride-sensitive channels in the renal tubule. The risk is greatest in the elderly and with use of high-dose TMP/SMX.

Table 10-2: Warfarin Interactions	
Most Severe	Possible
TMP/SMX	Quinolones
Erythromycin	Omeprazole
Amiodarone	Clarithromycin
Propafenone	Azithromycin
Azole antifungals	Prednisone
Metronidazole	Acetaminophen (> 1.5 g/d)

Statin Interactions

Statins are metabolized by the liver’s P450 system except pravastatin, which is metabolized by the kidney. The most life-threatening reaction to a statin is rhabdomyolysis. The risk is much greater when statins are combined with drugs that slow their metabolism. The drugs that affect statin hepatic metabolism are fibrates, erythromycin, cyclosporine, azole antifungals, protease inhibitors, verapamil, diltiazem, and amiodarone. Grapefruit juice will also markedly raise the blood levels of some statins by inhibiting initial hepatic metabolism. Lovastatin and simvastatin are most affected; pravastatin is least affected (because it is metabolized by the kidneys). The most common side effect of statins is myalgias.

Other Interactions / Side Effects to Know

Know:

- Rosiglitazone and pioglitazone cause edema, worsening congestive heart failure (CHF), and weight gain.
- Dihydropyridines (nifedipine, amlodipine) cause peripheral edema and constipation.
- SSRIs cause hyponatremia, sexual dysfunction, and may cause platelet dysfunction.
- Topiramate causes non-anion gap acidosis and kidney stones.
- Hydrochlorothiazide causes low K⁺, high Ca⁺, low Na⁺, and high uric acid.
- St. John’s Wort increases metabolism of statins, cyclosporin, some HIV/AIDS drugs, and oral contraceptives (→ treatment failure).
- NSAIDs increase risk of symptomatic CHF in patients at risk for coronary artery disease (CAD).
- Bisphosphonates can cause muscle and joint pain.
- PPIs may inhibit antiplatelet activity of clopidogrel (especially omeprazole) by inhibiting its transformation to the active metabolite in patients with CYP2C19 intermediate and poor metabolizers.

STATISTICS

SENSITIVITY AND SPECIFICITY

The Bayesian 4 Square

Note: T = true, F = false, P = positive, N = negative

Know statistics perfectly!

To make sense of the 4 square used in answering sensitivity and specificity questions, we will go over Figure 10-1. Let’s assume we have a group of cattle being tested for a deadly disease. They go through the testing station on the left and are directed to either the upper corral if their test is positive or the lower corral if their test is negative. All cattle are then driven across the corral to the right; but this disease is so deadly, all the diseased cattle die before they get to the far right of the corral. So we are left with 4 sets of cattle. The 4 square is very

Quick Quiz

- Define first-order kinetics.
- How long should you wait before rechecking a blood level for a drug that follows first-order kinetics?
- You have invented a test that is 90% sensitive and 95% specific for screening of breast cancer. If you tested 100 women with known breast cancer, how many would the test say have breast cancer (true positives)?
- Be able to fill in a 4 square and quickly determine sensitivity, specificity, PPV, and NPV.
- Which of the following take into account disease prevalence: sensitivity, specificity, PPV, NPV?

useful in determining sensitivity, specificity, and positive and negative predictive values.

Sensitivity and specificity try to account for those with (sensitivity) disease and those without (specificity) the disease.

Sensitivity takes into account only those who **have** the disease. Sensitivity = true positives (# of patients **with** disease who test **positive**) divided by the total # of patients with disease (those who test positive **plus** the false negatives). Sensitivity = $TP/(TP + FN)$ (Figure 10-1). Note that $(1.0 - \text{sensitivity}) = \text{false-negative rate}$. This implies that among patients with disease, there are some who test negative. Hence the mnemonic “SNOUT” (SeNsitive tests help rule OUT disease because the false-negative rate is low).

A good **screening** test should try to approach 100% but usually does not because there are some patients who have the disease but do not test positive (false negatives). SNOUT!!

Specificity takes into account only those who do **not** have the disease. Specificity = true negatives (# of patients **without** disease who test negative) divided by the total # of patients without the disease (those who test negative **plus** the false positives). Specificity = $TN/(TN + FP)$. Note that $(1 - \text{specificity}) = \text{false-positive rate}$. This implies that among patients without disease, there are some who test positive. Hence the mnemonic “SPIN” (SPecific tests help rule IN disease because the false-positive rate is lower).

A good **confirmatory** test should try to approach 100% but usually does not succeed—because some without the disease will test positive (false positives). SPIN!!

To help remember: Note that **sensitivity** takes into account only those who **have** the disease, and **specificity** takes into account only those who do **not** have the disease. This means that sensitivity and specificity are **independent** of the **prevalence** (percentage) of the population with the disease! Sensitivity and specificity are properties of the test itself.

The “positive predictive value” (PPV) of a diagnostic test is the probability of disease in a patient given a positive test—i.e., $PPV = P(\text{disease} | \text{positive test})$. To figure this, you take into account the numbers of both the true positives and the false positives. This combination **does** reflect prevalence. The positive predictive value is generally higher with conditions that are more prevalent (common) than with conditions that are less prevalent (rare), given the same sensitivity and specificity of a test. The formula is $PPV = TP/(TP + FP)$. This makes sense:

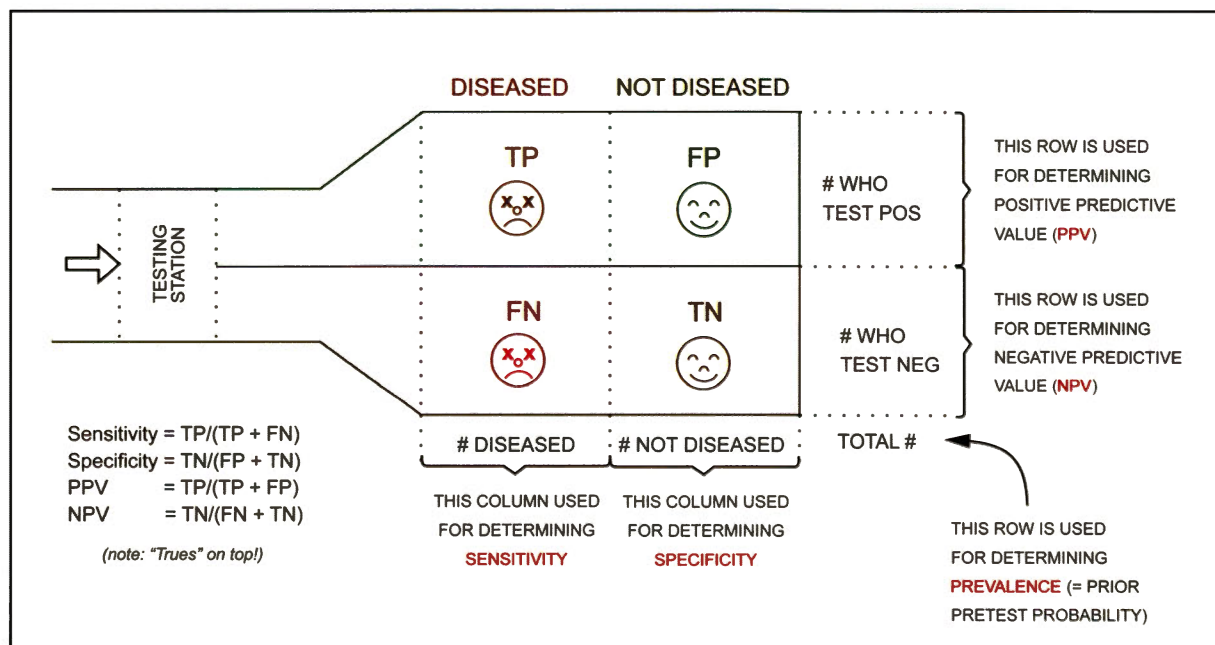


Figure 10-1: The Bayesian 4 Square

Table 10-3

	Disease	No Disease	Total
Abn tests	TP	FP	TP + FP
NI tests	FN	TN	FN + TN
Total	TP + FN	FP + TN	

Table 10-4

I. Sketch this first:

	With	Without	Total
Abn tests			
NI tests			
Total			

Table 10-5

II. Based on the given information:

	With	Without	Total
Abn tests	1	3	13,000
NI tests	2	4	987,000
Total	5,000	995,000	1,000,000

Note that the 5,000 and 995,000 are the **denominators** in the sensitivity and specificity equations!

Table 10-6

III. Calculations

	With	Without	Total
Abn tests	4,950	8,050	13,000
NI tests	50	986,950	987,000
Total	5,000	995,000	1,000,000

true positives divided by all those who test positive! If a disease is rare, even if the sensitivity and specificity are high, the false positives may greatly outnumber the true positives, making the chance of having the disease with a positive test (PPV) much less. This is one of the main factors used to determine whether a screening program is feasible.

The “negative predictive value” (**NPV**) of a diagnostic test is the probability of not having a disease given a negative test; i.e., $NPV = P(\text{no disease} | \text{negative test})$. Using the 4 square, the formula is $TN / (TN + FN)$. NPV, like PPV, reflects the disease prevalence. The negative predictive value is generally higher with conditions that are less prevalent (rare) than with conditions that are more prevalent (common), given the same sensitivity and specificity of a test.

Tips:

- Note that in all the above (sensitivity, specificity, PPV, NPV), the “Trues” go in the numerator (on top).
- PPV deals with nothing but positives; NPV deals with nothing but negatives (in terms of test results).
- Sensitivity deals with positives; specificity deals with negatives (in terms of disease status).

The prevalence (or prior/pretest probability) is merely the fraction of the population who has the disease. This is $(\text{Total with disease}) / \text{Total}$, or $(TP + FN) / [(TP + FN) + (FP + TN)]$.

Not all the data may be given in a question asking you to find sensitivity, specificity, PPV, NPV; it is **very** useful to use Table 10-3 in its stripped-down form (Table 10-4). You insert the given values and then calculate for the blank spaces!

The “givens” in the following example are filled in. When all the spaces are filled in, the question is easily answered. Know this stuff!

Example: Incidence of cancer is 1/200 in a population. In a test under consideration, if sensitivity = 99% and the frequency of abnormal tests in the population is 1.3%, what is the ratio of false positives to true positives—and is this a good screening test? To solve, first draw the Table 10-4 and fill in the given numbers. This gives us Table 10-5.

If the population is not given, assume 1 million. 1/200 incidence gives 5,000 total persons **with** cancer. $0.013 \times 1 \text{ million}$ gives 13,000 total **abnormal** tests. Then just subtract to find the number without cancer (995,000) and the number of normal tests (987,000). Note that the 5,000 and 995,000 are the **denominators** in the sensitivity and specificity equations!

Then we find the other blanks in the order shown 1, 2, 3, and 4. Blank (1) is the only one requiring thought:

$$\text{Sensitivity} = TP / (TP + FN) \text{ or } 0.99 = TP / 5,000$$

$$\text{So: } TP = 4,950.$$

The others are found by subtraction (Table 10-6).

Once you have the entire matrix filled in, you can solve **any** problem, provided there is enough information. In this example, $PPV = TP / (TP + FP) = 38\%$ —**not** a good percentage for a screening test! If data given to solve the problem are insufficient, it will become apparent when you are unable to fill in all the blanks.

What happens if you change the criteria for what is called a normal test? If you increase the range for what is normal, you will get more **negative** tests—both true negatives and false negatives. This will decrease the sensitivity while increasing the specificity.

Why is this? Assume we did this for the previous example. Because the numbers of people with and without the disease (prevalence) remain the same, the denominators in the sensitivity and specificity equations remain

Quick Quiz

- Define positive and negative likelihood ratios in terms of sensitivity and specificity.
- You read that a study shows a new treatment for lung cancer improves survival by 60% and the p value for the study is 0.2. Based on these results, would you recommend this treatment?
- What is the cutoff p value that is considered statistically significant?

the same—but the numerators change. In the sensitivity equation, the **numerator decreases** (decreased TP due to increased FN), so **sensitivity decreases**; i.e., fewer of those with the disease are found by the test. In the specificity equation, the **numerator increases**, so **specificity increases**; i.e., those testing negative are less likely to have the disease. In the specificity equation, the numerator increases, so specificity increases; i.e., those testing negative are less likely to have the disease.

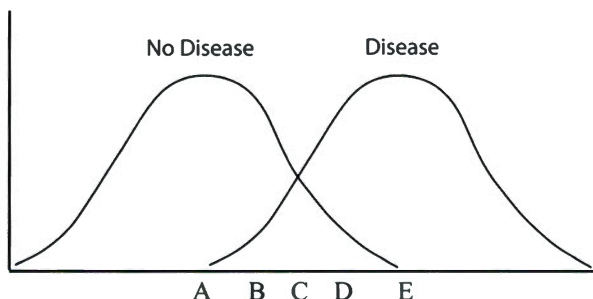
As a quick tip, think of the threshold for normal on the test as being the line in the 4 square that divides the top from the bottom: As the threshold increases, the line rises, indicating decreasing numbers of TP and FP and increasing numbers of FN and TN. As the threshold decreases, the line goes lower, indicating increasing positives and decreasing negatives. Because the denominator in the sensitivity and specificity formulas stay the same, just see what happens to TP and TN. If TP increases, sensitivity increases. If TN increases, specificity increases.

You will also see that anytime the test normals are redefined, sensitivity will increase **at the expense** of specificity and vice-versa.

As disease prevalence and incidence decrease, the number of false positives increases while the number of false negatives decreases—so the ratio of false positives to false negatives increases. This occurs because there is no change in the sensitivity or specificity of the diagnostic test.

Sensitivity, specificity, PPV, and NPV can also be interpreted from diagrams such as these:

This chart shows test performance for a diagnostic test in 2 populations, 1 with the disease and 1 without.



Remember that sensitivity = [True positives/(True positives + False negatives)]. Point A would have no false negatives, since all of the group with the disease would have a value greater than A. Thus, Point A has the best sensitivity. Point A also has the best false-negative value. Point E has no false positives and would have the best specificity and the best positive predictive value.

The last thing we'll deal with here is positive and negative likelihood ratios:

Positive Likelihood ratio = Sensitivity / (1 – Specificity). The positive likelihood ratio is used with positive test results; i.e., the probability of a patient who has the disease testing positive divided by the probability of a person not having the disease testing positive. For example, if the presence of peripheral edema has a sensitivity of 80% and a specificity of 40% for the presence of cirrhosis, what is the likelihood ratio if a patient has edema? Plugging in the numbers: $(.8)/(1 - .4) = (.8)/(.6) = 1.33$.

Negative Likelihood ratio = (1 – Sensitivity) / (Specificity). Use this when you have a negative test result and you are looking to see how much less likely something is with a negative test. For example: If the absence of peripheral pulses has a sensitivity of 90% for PAD and a specificity of 95%, what is the negative likelihood ratio for PAD if a patient has peripheral pulses? Plugging in the numbers $(1 - .9)/(.95) = (.1)/(.95) = .105$.

P Value and Confidence Intervals

The p value is a way of expressing a study's **statistical significance**. Suppose a randomized trial compares 2 drugs and concludes that drug A is better than drug B. The smaller the p value, the more confident we can be that drug A really is better than drug B—and that this is not simply a chance occurrence. Thus, if a study has a p value of 0.05, the likelihood that the results are due to chance is only 1 in 20 (= 5%; or $p = 0.05$). P values of less than 0.05—such as 0.01 or 0.001—imply even **greater** statistical significance. A p value ≤ 0.05 is considered statistically significant.

The above ($P < 0.05$, ha!) is probably all you need to know for most questions on p values, but you should know more of the theory. P value is the probability of the result in question occurring, assuming that the distribution of occurrences used for the calculations is correct. Let's do a rough "for instance." Say you normally see 1 case of giardiasis in your office per week. Then, one week you see 4 cases and you wonder if an epidemic of giardiasis has started. How often should you see 4 cases a week if you normally see only 1 case per week?

What you assume is chance variation results in a mean (average) incidence of giardiasis of 1 case per week and that the variation in occurrences is "per" a

certain distribution. This is generally called the “null” or “chance” hypothesis. The distribution can be plotted from thousands of cases, or we can further assume it follows a standard distribution, such as the Poisson distribution. **Assuming this is correct**, what is the probability of 4 cases occurring in one week? What you do is go to a table that displays various values of the distribution and read the p value off the table. In this case, $P = 0.019$.

The way to read this: “Assuming that the average incidence of giardiasis is 1 case per week and further assuming that the weekly incidences of giardiasis fit into a normal Poisson distribution, then the probability of 4 cases per week occurring by chance is 1.9%.” This seems small, and it is, but it does mean that you can expect to see 4 cases per week about once per year (if the assumptions are correct!). Now, if you see 4 cases again the following week ...!

Type 1 and Type 2 Errors

These relate to statistical hypothesis testing. There is a null hypothesis, and then there is an alternate hypothesis (The null hypothesis is not true.)

Type 1 = concluding that there is a difference (reject null hypothesis) when there is no difference. In other words, it is the **chance of a false positive result**. This chance is typically expressed by the **p value**. This reflects the willingness of the investigator to declare a benefit when there is none. You can think of this as similar to the argument for specificity of a study and how it can be used to rule in a true effect. (Remember SPIN.)

Type 2 = concluding that there is no difference (accept null hypothesis) when one exists. In other words, this is the **chance of a false negative result**. This is the likelihood that the trial will miss a true difference between the two test groups.

The power of a study (1 minus the type 2 error value) is similar to the argument for sensitivity of a study. It tells you the likelihood of ruling out a true effect. (Remember SNOUT.)

Suppose a study shows no difference between experimental groups. If the power is set at the typical 80% level, the chance of type 2 error is 20%. In other words, you’ll be wrong 1 out of every 5 times the same study is done. If you increase the power of the study to 95%, the false-negative rate is now 5%. This gives you a little

more confidence in the negative result because it is less likely to be falsely negative.

Meta-Analysis

Meta-analysis is the retrospective analysis of many studies (essentially a mathematical systematic review) concerned with the same topic. There are several methodological flaws and biases involved with meta-analyses, as well as several severe statistical restraints. Compiling studies with differing type 1 and type 2 errors is difficult. Other areas of difficulty include ages of participants and assumptions of the magnitude of differences expected among the experimental groups. These factors, which lead to methodological heterogeneity, can result in statistically significant heterogeneity in the results. Unfortunately, absence of statistical evidence is not necessarily evidence of absence of heterogeneity because methodological heterogeneity simply couldn’t be detected using the surrogate of statistical heterogeneity.

Confidence Interval Charts

Confidence interval (CI) charts are frequently used in meta-analyses—which are when results from all available relevant studies are analyzed together for greater statistical power.

A CI of 95% is essentially the same as a $P < 0.05$. A CI of 99% is similar to $P < 0.01$. In the first case, it reflects the spread of 95% of the data points measured. In the second, it reflects 99% of the spread of the data points. A consistent result that falls outside the confidence interval of 95% or 99% may be considered so unusual as to be “statistically significant.”

Look at the charts (A–D) in **Figure 10-2** through **Figure 10-5**. Pay attention to the **vertical** dotted line, which always means **no effect**. In figures A and B, the vertical dotted line represents **no response to treatment**. In C and D, the vertical dotted line is equal to an **odds ratio** of 1 (again, no effect). In other representations, the vertical line may be given a specific number that represents the mean from the entire population or from controls.

Each plotted solid **horizontal** line on these charts represents the 95% confidence interval from one study.

The null hypothesis (no difference in treatment outcomes) is being tested in each figure. If the difference between treatment x and treatment y is assumed to be

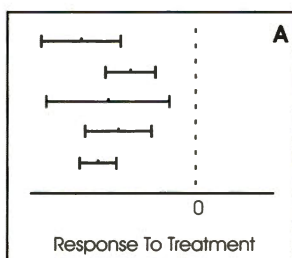


Figure 10-2

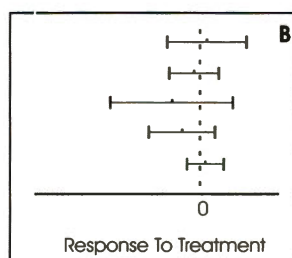


Figure 10-3

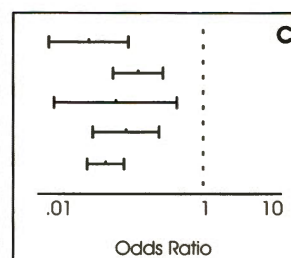


Figure 10-4

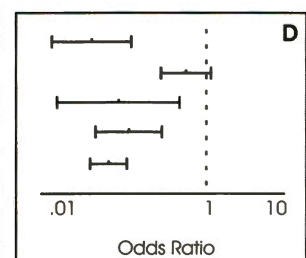


Figure 10-5

Quick Quiz

- A study shows a newer treatment for lung cancer improves survival by 5%, and the 95% confidence interval for the study is 1.6 to 4.9. Assuming treatments have the same side effects, would it be worthwhile to consider the new treatment?
- Be able to calculate the NNT.

zero, but 95% of the time the difference is less than (or greater than) zero, then there must be a difference in treatment outcomes that can't be ignored—that is statistically significant.

The null hypothesis can also be expressed as a ratio, in which case, because treatment outcomes are assumed to be the same, then the ratio between treatment group x and treatment group y is 1 (no difference). In this case, the vertical line is shown with a value of 1.

So, if the "95% confidence interval" does **not** cross the vertical line, then the results are considered significant. For example, if you are reviewing a trial looking at response to treatment (i.e., vertical line = 0) and see that the 95% confidence interval is 0.5 to 1.9, you know the study shows a significant response. However, if the 95% confidence interval is -0.7 to 1.6, then it is a nonsignificant result!

Note that the charts depicted here could also be shown in a vertical format—with a horizontal dotted line representing the 0 or 1. Look at the chart sideways to see what this looks like!

Let's go over these charts so you will know at a glance how to interpret them:

- Chart A is a meta-analysis with each study showing a significant response to treatment.
- Chart B shows a similar meta-analysis in which not even one of the studies shows a significant response to treatment.
- Chart C shows a significantly different odds ratio in all studies reviewed. Odds ratio is a way of comparing whether the probability of an event is the same for 2 groups—usually comparing a control group and the study group (1 = same odds).
- Chart D shows 1 study with non-significant results but 4 others with significant results; therefore, the meta-analysis will show an overall significant result.

Number Needed to Treat

This helps us make the leap from statistical significance to clinical significance.

The number needed to treat (NNT) is the number of people who **need to be treated** for a period of time to prevent 1 event. NNT is calculated by taking the inverse of the absolute risk reduction between intervention and control groups.

Example: A new drug is studied to see if it can reduce heart failure mortality. Mortality in the treatment arm (active drug) was 10/100, while mortality in the placebo arm was 30/100 during a 4-year follow-up with a p value of $< .001$. So, this is statistically significant. Clinically, you want to know how useful this is going to be for patients.

$$\text{NNT} = 1 / (30/100 - 10/100) = 1 / (0.3 - 0.1) = 1 / 0.2 = 5$$

This means 5 patients must be treated for 4 years to prevent 1 death.

Alternatively, NNH means number needed to harm. It is the number of patients who get a drug or intervention for each patient harmed.

Note also the difference between relative risk reduction and absolute risk reduction. This drug has a relative risk reduction of 66.7% ($0.2/0.3$) and an absolute risk reduction of 20%. Both reflect clinical significance, but relative risk is sometimes used preferentially. If the treatment and mortality numbers were to be changed to 1/100 and 3/100 respectively, the NNT would change from 5 to 50 because the absolute risk reduction is now 2% instead of 20%. But the relative risk reduction is still 66.7%!

OSTEOPOROSIS

OVERVIEW

Osteoporosis is decreased bone strength predisposing patients to bone fractures. Patients who get osteoporosis are postmenopausal females or both men and women with certain predisposing diseases, risk factors, and/or behaviors.

Most fragility fractures are in those without osteoporosis by radiographic methods.

Primary prevention of osteoporosis has become very controversial with the 2012 USPSTF update (currently released for public comment so the final draft may change). In its current form, the document says that evidence is insufficient to recommend for or against giving vitamin D and calcium supplementation to women or men for primary prevention of osteoporosis. In contrast, the 2010 National Osteoporosis Foundation guidelines recommend vitamin D and calcium supplements to prevent fractures in all adults 50 and older. Of note is that recent USPSTF guidelines show that giving vitamin D supplementation does prevent falls in adults 65 and older, but the newest guideline says that it does not prevent fractures. From a Board standpoint, it is reasonable to accept that vitamin D supplementation is recommended to prevent falls and that evidence is insufficient at present to recommend for or against vitamin D and calcium supplementation for primary prevention of osteoporosis.

Osteoporosis is common in the elderly and generally suspected by clinical presentation. (Fragility fracture is a clinical diagnosis if postmenopausal.) There are many risk factors for primary osteoporosis, but these have the highest known risk:

- Age
- Personal history of fragility fracture (no trauma or from fall less than standing height)
- History of fragility fracture in 1st degree relative
- Weight less than 127 lbs or BMI < 21
- Alcohol intake of 2 or more drinks/day
- Menopause before age 40
- Current or previous use of glucocorticoid therapy: > 3 months at a dose of > 5 mg/d of prednisone
- Cigarette smoking

Patients with the following conditions should be screened regardless of age and gender:

- GI diseases (UC, Crohn's, celiac, gastric bypass, malabsorption)
- Endocrine disorders (hyperparathyroidism, Cushing syndrome, hypogonadism, hyperthyroidism)
- Medications (glucocorticoids, thyroxine over-replacement, lithium, phenobarbital, phenytoin, cyclosporine)
- Rheumatoid arthritis, SLE
- Anorexia nervosa
- Prolonged bed rest or wheelchair bound

The most significant x-ray findings are multiple vertebral compression fractures (2/3 of vertebral fractures are painless).

The 3 most accurate methods of diagnosis (by determining loss of bone mineral density):

- 1) Quantitative CT
- 2) Dual photon absorptiometry (DPT)
- 3) Dual energy x-ray absorptiometry (DXA, previously DEXA)

Quantitative CT scan gives a larger dose of radiation and is more expensive. CT scan and DPT take a lot of time. **DXA** is the preferred method. It is the quickest (about 15 minutes), the least expensive, and the **most accurate!** Precision of DXA is +/- **1–2%**, whereas precision of DPT is +/- 2–5%.

Bone mineral density (BMD) reports usually have 2 results: the T-score and the Z-score. The T-score compares results with normal, young, healthy bone; a T-score of –1.0 means the BMD is 1 standard deviation (SD) less than normal—about 10% low. A T-score of **–2.5 or lower** is the definition of osteoporosis (about 25% below normal), whereas those between –1 and –2.5 suggest osteopenia. The Z-score compares the BMD result to age- and sex-matched controls and is now recommended for use in men and women < 50 years of age.

The Z-score is **not** used for treatment but rather to see if there is **accelerated osteoporosis**, which would suggest secondary factors—such as drugs—might be involved.

The National Osteoporosis Foundation, in collaboration with multiple organizations, implemented new guidelines in 2008 and confirmed in 2010 that recommend screening **all women age 65 or older and all men 70 and older** with DXA scans, and selectively screening women and men > 50 years if they have **any** osteoporosis risk factors, particularly those listed above.

The 2010 National Osteoporosis Foundation guidelines recommend that **drug therapy** should be considered in postmenopausal women and men > 50 years of age presenting with these findings:

- A hip or vertebral fracture
- T-score between –1.0 and –2.5 with other prior fractures (not hip or vertebral)
- T-score < –2.5 (Remember: This means a score like –3.0, –2.7, etc.; we are dealing with “less than” and negative numbers.)
- T-score between –1.0 and –2.5 and secondary causes associated with high risk of fracture (steroid use or total immobilization)
- T-score between –1.0 and –2.5 and a 10-year probability of hip fracture > 3% or a 10-year probability of **any** major osteoporosis-related fracture > 20% based on the U.S.-adapted WHO algorithm (These probabilities require calculations at www.shef.ac.uk/FRAX.)

Universal recommendations for all patients (regardless of age or risk factors) with osteoporosis:

- Dietary calcium of 1,200–1,500 mg/day (include supplements if necessary, but higher amounts are not recommended due to increased risk of kidney stones and cardiovascular disease)
- RDA for those without osteoporosis (Up to age 70 get 600 IU vitamin D/day; > 70 years of age: 800 IU vitamin D/day.)
- Regular weight-bearing exercise
- Fall prevention
- Avoid tobacco
- Avoid excess alcohol use (< 2 drinks/day)

DRUG THERAPY FOR OSTEOPOROSIS

All drugs that increase bone density do so by affecting bone remodeling. They can either increase the buildup (stimulate osteoblasts) or decrease breakdown (inhibit osteoclasts). A categorization of the drugs, which is based on these effects on bone remodeling, is anabolic vs. anticatabolic. Anabolic agents stimulate both osteoblasts and osteoclasts but stimulate the osteoblasts more, leading to a net increase in bone building and increased bone density. Anticatabolic agents inhibit osteoclasts, thereby decreasing the resorptive process.

Quick Quiz

- What are the risk factors for osteoporosis?
- How do you screen for osteoporosis?
- How are the Z-score and T-score used in the evaluation of osteoporosis?
- Who should be treated for osteoporosis?
- What are the recommendations for all patients with osteoporosis?
- A patient on alendronate presents with difficulty swallowing. What is the likely etiology?
- What is the most serious consequence of osteoporosis?

Anabolic agents (stimulate osteoblasts): Parathyroid hormone (teriparatide) is currently the only one available. Teriparatide can be used for only 2 years (because of cumulative increased risk of osteosarcoma), and, once discontinued, patients need to use a bisphosphonate.

Anticatabolic agents (inhibit osteoclasts) includes the rest of the osteoporosis drugs:

- HRT (hormone replacement therapy)
- Bisphosphonates
 - Oral bisphosphonates: alendronate (Fosamax®), ibandronate (Boniva®, also available in IV form, see next), risedronate (Actonel®)
 - Injectable bisphosphonates: ibandronate and zoledronate (Reclast®)
- Calcitonin salmon
- Raloxifene (Evista®)

A few notes on these drugs:

Teriparatide is the only anabolic agent currently available. Parathyroid hormone causes both an increase in bone buildup and an increase in bone resorption—but the net effect is to build more bone than it breaks down.

HRT may prevent or reverse the development of osteoporosis, **but** its use in the peri- and postmenopausal woman is a two-edged sword. Most recommend **not** using HRT as 1st line therapy! See HRT on [page 10-14](#).

Bisphosphonates are analogs of pyrophosphate and, like estrogen and other anticatabolic agents, **inhibit bone resorption**. Bisphosphonates and HRT appear to have an **additive effect**. They effectively act as antagonists of parathyroid hormone, which causes resorption—a release of calcium from the bone into the serum.

Bisphosphonates, especially IV, have been associated with osteonecrosis of the jaw. Use caution if using these drugs in patients who will be having extensive dental surgery. Another very important side effect is severe muscle/

joint/bone pain. Odd fractures of the long bones (femur) have been reported in patients receiving bisphosphonates.

The bisphosphonates are:

- Alendronate is an option when a patient is uncomfortable with HRT or HRT is contraindicated. Alendronate is both poorly absorbed and a rare cause of severe esophagitis (although this is less of a problem with weekly dosing); the patient must carefully follow the recommendations to take it with a full glass of water on an empty stomach and not eat or lie down for 30 minutes after ingestion.
- Risedronate was FDA-approved in April 2000 for the prevention and treatment of postmenopausal osteoporosis. It has the same clinical effect as alendronate but may have fewer GI side effects. Even so, take the same dosing precautions as with alendronate.
- Ibandronate is the first once-monthly medication approved for postmenopausal osteoporosis.
- Zoledronic acid is given by IV once a year.

Calcitonin salmon nasal spray at 200 mg/d increases bone mineral density and decreases risk of vertebral fractures. There is no evidence that it decreases hip fracture risk.

Raloxifene. During the development of antiestrogens, it was discovered that some substances that block the effect of estrogen on some tissues actually mimic estrogen on others! These are called selective estrogen receptor modulators (**SERMs**). Examples are tamoxifen and raloxifene. The effect of raloxifene on bone and lipid levels is similar to, but **less than, estrogen**; however, it exerts estrogen-antagonistic effects on the breast and uterus and **may** be less likely to cause cancer than traditional HRT. Raloxifene is FDA-approved for both prevention and treatment of postmenopausal osteoporosis.

Fractures are the most serious consequence of osteoporosis. There are 1.5 million fractures per year due to osteoporosis, with 300,000 of those due to hip fracture. Mortality due to hip fractures is about 20% within the first year! Femoral neck and intertrochanteric fractures account for 97% of hip fractures.

Femoral neck fractures are **intracapsular** and occur below the femoral head but above the trochanters. Displaced femoral neck fractures often disrupt the blood supply to the femoral head and result in osteonecrosis and/or nonunion; therefore, the treatment of choice is either femoral head replacement or total hip arthroplasty. Nondisplaced femoral neck fractures have a low incidence of osteonecrosis and nonunion, so these are usually treated with internal fixation using pins or screws.

Intertrochanteric fractures are **extracapsular** and are usually treated with internal fixation with a “sliding hip screw.”

In both types of fracture, the main goal is to achieve mobility and function as soon as possible, thereby

avoiding the morbidity and spiraling complications due to poor mobility.

Deep vein thrombosis (DVT) occurs in **48%** of hip fracture patients **without** anticoagulants. **With** anticoagulation, DVT occurs in **24%** and **27%**, respectively, for those on warfarin or subQ low-molecular-weight heparin.

Other complications of hip fractures are pressure ulcers, constipation, and fecal impaction.

GERIATRICS

DEMOGRAPHICS

Life expectancy correlates with race and gender. Caucasian women live the longest; in a tie for 2nd place are African-American women and Caucasian men. African-American men have the shortest life spans. Generally, women live longer than men, are less likely to remarry, lack money to take care of all their needs, and are more often disabled as they age.

60–84% of patients > 65 years old will have hypertension, and roughly 20% have diabetes. Cancer is now the leading cause of death in adults younger than 85 years (followed by heart disease and stroke). Many studies show that elderly patients are **not** offered the same life-saving procedures as younger patients with the same disease states, even though age has no adverse effect on outcomes of the interventions. Know that age alone is **not** enough of a reason to withhold an intervention.

If a patient lives to be 75 years old, he will most likely live to age 86. And those who live to 85 years are likely to live to age 91.

“Frailty” affects a large number of elderly patients. It can be caused by comorbid illnesses and/or disability but not necessarily so. Frail patients are more likely to fall, become disabled, or die. Make a diagnosis of “frailty” if ≥ 3 of the following are present:

- 1) Unintentional loss of ≥ 10 lbs/1 year
- 2) Exhaustion due to lack of endurance
- 3) Decreased hand strength
- 4) Walking slowly
- 5) Reduced activity

ASSESSMENT

All geriatric patients should have a specific interval assessment of “function” because functionality is related to longevity. Functional assessment evaluates several components:

- Activities of daily living (ADLs)
- Instrumental activities of daily living (IADLs)
- Cognition
- Hearing
- Vision
- Gait and balance
- Nutrition (discussed separately)
- Driving ability

Start by assessing ADLs: Can the patient dress, bathe, feed, use the bathroom, and move around without help? IADLs are those activities that connect the patient with the community: Can she manage her money, take her own medication, manage transportation, make phone calls, do the shopping and housework, and make her meals?

Assessment of cognition looks for evidence of dementia and delirium.

Assessing dementia: A quick way is to use the Mini-Mental State Exam (MMSE) or the Mini-Cog (easier to remember) to assess dementia. To perform the Mini-Cog, ask the patient to remember 3 words, and then ask him to draw a clock showing a specific time. After he’s drawn the clock, ask him to recite the 3 words. Score by giving 1 point for each word remembered correctly and 2 points for an accurate clock (0–2 = dementia).

Assessing delirium: The best tool to assess delirium is the Confusion Assessment Method (CAM; 94–100% sensitive; 90–95% specific). See Table 10-7. Delirium is present when patients have features 1 and 2 with either 3 or 4.

More on delirium and dementia on page 10-15.

Hearing and vision can be assessed using traditional instruments such as the whisper test and the Snellen eye chart. The whisper test is performed by covering the ear that is not being tested, then whispering a question while standing about 2 feet away. If the patient responds correctly, then no more testing is required. Give the patient 6 tries. Refer for further audiometric testing if the patient answers 3 or more questions (out of 6) incorrectly.

Table 10-7: Delirium Assessment Tool—Confusion Assessment Method	
Feature 1	Acute onset and fluctuating course: Is mental status acutely changed from baseline, and does the change fluctuate throughout the day?
Feature 2	Inattention: Is there a problem focusing attention (e.g., easily distracted)?
Feature 3	Disorganized thinking: Is conversation rambling or irrelevant? Are ideas illogical in flow?
Feature 4	Altered level of consciousness: Is the patient alert (normal state), hyper-alert, drowsy but easily aroused, difficult to arouse, or unarousable?

Quick Quiz

- How do you diagnose “frailty”?
- What assessments should be done periodically in elderly patients?
- What are the major features of delirium, using the Confusion Assessment Method?
- What are the criteria that diagnose malnutrition?
- Which factors, associated with aging, predispose patients to imbalance and falls?
- What are risk factors for falls in the elderly?

Gait and balance are assessed well with the timed Get-Up-and-Go test. Have the patient get up from a chair and walk 10 feet, then turn around and come back to sit. If it takes him longer than 20 seconds, then he is at high risk for falls; 10–20 seconds puts him at moderate risk. More specifics about falls in Mobility and Gait below.

Know that elderly (and teens) have more driving violations compared to the general population. Usually, patient performance on the vision, hearing, and gait assessment will give you an adequate assessment of a patient’s ability to operate a vehicle. Formal assessment is offered for the elderly through departments of motor vehicles.

NUTRITION

We become less active as we age, and we lose muscle and body fat (more muscle than fat). Nutritional requirements are reduced, so generally, older people eat less. Malnutrition is still an issue for them, though, because of declining abilities and comorbid systemic disease.

Malnutrition is diagnosed in any of the following circumstances:

- Unintentional weight loss of ≥ 10 lbs/6 months
- BMI < 22
- Albumin < 3.8 g/dL
- Cholesterol < 160 mg/dL
- **Any** vitamin deficiency

When malnutrition is diagnosed, thoroughly assess for modifiable risks; e.g., decreased access to nutritious food, denture or teeth problems, untreated medical illness, inability to perform IADLs such as grocery shopping.

The declining appetite and energy needs with aging are associated with a natural replacement of carbohydrates for fats. Counsel geriatric patients to increase their daily fluid and fiber intake and to eat healthy fats (monounsaturated and omega-3s) such as olive oil, nuts, avocados, and fish. Vitamin supplements are useful in patients who are poor eaters because this age group is especially vulnerable to deficiencies of vitamin D, B₁₂, and calcium.

The National Institute on Alcohol Abuse and Alcoholism and the American Geriatrics Society have recommendations on healthy alcohol intake for people older than 65 years—no more than 2–3 drinks/day and/or 7 drinks/week, with lower amounts for people taking meds with side effects that are potentiated by alcohol.

MOBILITY AND GAIT

Falling

Age is associated with **increased instability and falls**. 50% of patients age 80 and older fall each year! The elderly have a stiffer, less agile gait with decreased position reflexes. 5% of falls result in fractures and, if the patient cannot get up, possibly hypothermia and dehydration.

Aging is associated with decreased proprioception and baroreceptor reflexes, so orthostatic hypotension and swaying is common. There is also an increased incidence of postprandial falls in the elderly—probably due to hypotension from ingestion of carbohydrates.

The major **predictor** for fracture from a fall is **osteoporosis**.

Risk factors for falls:

- Age
- Female gender
- Past history of falls
- Rugs, untidiness, and dim lighting in the home
- Poor vision
- Orthostatic hypotension
- Unsteady gait
- Cognitive impairment
- Musculoskeletal disease
- Cardiovascular disease (e.g., syncope)
- Psychotropic drug use

The **drugs** most commonly implicated are benzodiazepines, antidepressants, neuroleptic agents, and blood pressure medications. Know that using forms of physical restraint **increases** the risk of serious falls and injuries, so avoid physical restraints when possible.

There are 5 quick office tests that can be done to assess the risk for fall in the elderly:

- 1) Timed Get-Up-and-Go test (see Assessment above)
- 2) Gait speed (slower = $\uparrow$ risk)
- 3) Tandem (heel-to-toe) walk
- 4) Visual acuity
- 5) Calf circumference (smaller = $\uparrow$ risk)

Workup for the patient with falls includes a good history and physical exam, with emphasis on a multidisciplinary assessment and evaluation for a cardiovascular cause. Do a syncope workup if the patient does not remember the fall or if the history is suggestive. Also think about weakness associated with osteomalacia as a

cause—especially in nursing home patients who are bedridden and never get in the sunshine. Check 25-(OH)₂-D if you suspect osteomalacia, and treat deficiency if found because treatment decreases fall risk.

Anticipatory guidance for falls may include restriction of certain activities, improving the lighting at home (use night lights), decreasing hazards (remove rugs and loose carpets), and placing extra supports (bars in the shower). Exercise (especially focused on balance and resistance training) is **very important** in helping patients maintain mobility and strength, reduce falls, and prolong survival.

Immobility

Patients **adapt** to bedrest; and the longer a patient is immobilized, the harder it is to ambulate again. Immobilization causes decreased ADH secretion → diuresis → decreased blood volume → orthostatic symptoms. Also, immobilization causes muscle atrophy. The heart continually deconditions after 2 days of bedrest. The elderly are more affected by bedrest because they have less reserve than young people. Treat with rehabilitation.

Know that prolonged immobility is associated with development of hypercalcemia (although this is more common in teens and young adults after traumatic immobilization). The hypercalcemia improves with mobilization.

Decubitus Ulcers

Sustained pressure over a prominent bone is the main etiologic factor. Shearing and friction tear the skin and cause necrosis with ulceration. **Moist** environments (notably, urinary incontinence) increase the risk. Know that decubiti in **nursing home patients** increase their mortality (usually from osteomyelitis and bacteremia/sepsis). Also know that malnutrition (≥ 10 lb weight loss in past 6 months) increases the risk for development of ulcers.

There are 4 stages of decubitus ulcerations.

- Stage 1 is nonblanching erythema (reddish macules).
- Stage 2 is partial-thickness skin loss (small superficial ulcer).
- Stage 3 is full-thickness skin loss.
- Stage 4 is loss of tissue down to the muscle, tendon, or bone.

Most common places that pressure ulcers occur are the heels, trochanter, sacrum, and iliac crest.

Bed-bound patients should be rotated from side to side (30-degree angle) every 2 hours. This prevents contact against bony prominences mentioned above. Special mattresses and heel/elbow pads also help, but it's controversial whether most interventions actually prevent ulcers.

In established ulcers, keep pressure off the area; and if an eschar exists, remove it for proper staging. The workup then includes determining whether any arterial

or venous insufficiency exists and treating any infection or maintaining a “clean” ulcer.

Infected ulcers require debridement of necrotic tissue back to healthy granulation tissue, using either “chemical” topical treatments or a scalpel.

Next, the wound has to be cleaned and dressed properly. Know that **saline cleansing** is best because it is gentle on growing tissue, and that iodines or peroxides kill tissue if used repeatedly. The choices for wound dressings are wide and variable. Follow the advice given by the wound care physical therapist. Know wet-to-dry dressings as a means for debriding wounds have fallen out of favor because they too often damage friable new tissue.

Give antibiotics, in addition to local wound care, if the patient is systemically ill. Use deep wound cultures to guide your choice.

Wounds will **not** heal in malnourished patients, so strictly follow the recommendations of the nutritionists to provide adequate increased nutrition.

Know: Wounds that develop in the setting of arterial or venous insufficiency will **not** heal unless the local blood flow is corrected—most often via surgical intervention. Sometimes this is feasible, sometimes not, depending on the patient's comorbidities.

Stage 1 and 2 ulcers heal quickly, but stages 3 and 4 usually take months.

IMMUNITY

Decreased immunity **is** age-related. Total T- and B-cell numbers stay the same, but the number of **CD4 T cells** **increases** with age, while the number of **CD8 T cells** **decreases** with age. Also, only **half** of the T cells remain competent, which is why herpes zoster and reactivation tuberculosis are often seen in the elderly.

PHARMACOLOGY

The elderly are very sensitive to drugs for the following reasons:

- Pharmacokinetics change with aging (changes in absorption and metabolism), which leads to increased concentrations of drugs.
- The volume of distribution for a drug increases because of the proportional increase of body fat compared to muscle.
- Excretion decreases, consistent with age-related decreases in renal and hepatic function.
- Pharmacodynamics of aging → **increased** effects of drugs, especially opioids and benzodiazepines.

General rules for medications in the elderly:

- Start meds at a **low dose**—usually about 1/2 the dose required for the general population and gradually titrate up to the normal therapeutic dose. If the patient

Quick Quiz

- How does immobilization affect serum calcium levels?
- What factors are associated with development of decubitus ulcers?
- What is the role of wet-to-dry dressings in decubitus ulcer treatment?
- What should you do for an elderly woman who is on chronic low-dose benzodiazepines for “nerves”?
- What is the average age of menopause?
- What is “andropause”?

gets into trouble at the therapeutic dose, try reducing the dose gradually—many elderly patients get satisfactory responses with subtherapeutic doses.

- **Any** adverse event should be assumed to be drug-related until proven otherwise.
- Always look to see if a prescribed drug is the cause of new symptoms before prescribing a new drug to symptomatically treat the new symptoms.
- Look at an elderly patient’s medicine record for prescription of an atypical antipsychotic (see Delirium on [page 10-15](#)) if he is institutionalized and falling. These are the most common causes of falls in nursing homes.
- Errors in self-administration increase dramatically once a patient is prescribed 3 or more medications. Elderly patients get very confused with pills that look alike and with distinguishing between generic and brand names.

Many elderly patients are dependent on low-dose benzodiazepines (BDZs) or narcotics. For these patients, you should attempt a slow withdrawal of these medications. These have often been mis-prescribed as treatment for anxiety, insomnia, depression, chronic pain, and drug withdrawal. Slowly taper following these general principles: Taper BDZs over 3–6 months after switching to an equivalent dosage of a water-soluble BDZ, such as oxazepam (slower onset, less addictive potential). With narcotic dependence, first determine the cause of pain (if any) and treat it with a non-narcotic drug (NSAID, acetaminophen). Avoid long half-life narcotics in treating geriatric pain.

Know that up to 75% of the elderly population in some studies use herbal supplements. Many do not divulge this information unless you ask directly.

ENDOCRINE

The only **specific** hormonal change that occurs with aging is ovarian failure: the average age of menopause is 51 years. The hypothalamic-pituitary-gonadal axis

is also disturbed in men, but not as predictably as in women. In both sexes, the adrenal zona glomerulosa declines in synthesis of DHEA, and the pituitary secretion of growth hormone wanes (and subsequently, also levels of IGF-1). Many other hormones are normal in the amount produced but do not function as well.

Many of these hormone perturbations are felt to be associated with the aging process, but **none** are conclusively linked. Growth hormone reduction appears to be associated with loss of muscle mass and strength. But supplementation is not encouraged because it is associated with too many side effects.

The pineal gland does not produce melatonin normally, and this may cause poor sleep and insomnia. Some patients are helped with melatonin supplementation.

Aging patients have a reduction in the clearance of thyroid hormone, so replacement hormone for hypothyroidism can be started at a lower dose. TSH increases with age, especially in women (see the Endocrinology section, Book 4); but at this time, a rising TSH without an accompanied decrease in T4 does **not** merit treatment for hypothyroidism.

Testosterone production decreases in men with age, but the effect is variable. However, the **rate** of sperm production is stable from ages 20 to 70 years! FSH and LH also decline but disproportionately compared to the more drastic decline in testosterone. The low testosterone production is most likely due to declining testicular function and not to hypothalamic disease.

Low testosterone is believed to be related to the following, although direct causation has not been proven:

- Decreased sexual function
- Decreased bone mineral density
- Decreased muscle mass (and increased fat)
- Decreased muscle strength
- Decreased mentation

The collection of the above, in association with reduced free testosterone, is called “andropause.” The Endocrine Society has guidelines (2006) for treatment of certain males with andropause who have symptoms and a serum testosterone < 200 ng/dL, with a treatment goal of 300–400 ng/dL. In spite of this recommendation, there are no good studies that prove a treatment benefit. Do **not** screen elderly men and do **not** treat men with low levels if they do not have symptoms.

Vitamin D deficiency is common because of decreased intake, decreased absorption, reduced sun exposure, and poor conversion of the storage to active form of vitamin D. Vitamin D intake in patients older than 70 years should be at least 800 IU/day, and many patients probably should be getting supplements. Decreased calcium intake is also common. 1,200–1,500 mg of elemental Ca/day is recommended in patients 65 and older.

Bone

Osteoporosis

The majority of women > 80 years of age have osteoporosis. According to current guidelines (see Osteoporosis on [page 10-7](#)), women 65 years of age and older should be screened with the DXA scan at least once. If the patient has **any** risk factors for vitamin D deficiency (especially poor diet or lack of sun exposure), check stores by measuring 25-(OH)₂-D.

Paget Disease

Paget disease of bone occurs in about 1% of people > 40 years old in the U.S. It is usually diagnosed after discovering an isolated elevation of alkaline phosphatase in an asymptomatic person. The disease results from a mismatch of osteoclast and osteoblast activity (remodeling), causing changes seen on x-ray, bone scan, CT, or MRI in localized areas. The bones are more brittle, vascular, and larger—leading to arthritis, high-output heart failure, and nerve compression, respectively.

Etiology: viral trigger in a host with certain genes.

Diagnosis is strongly suggested by bone scan results. Patients with Paget disease have focal areas of marked increased uptake.

Treatment is not required in the majority of patients and is not curative **but** may be needed if heart failure, bone pain, nerve compression, or hearing loss develops.

Drugs used: Bisphosphonates (etidronate, pamidronate, and alendronate) given orally or IV are effective in the treatment of Paget disease. SQ or IM **calcitonin** has also been shown to be effective.

Diabetes

Aging is associated with **decreased** carbohydrate tolerance, shown as a slight increase in fasting glucose. And now we know that insulin sensitivity and production decline with age. Elderly patients with diabetes get the same micro- and macrovascular complications as younger patients, but the elderly have to be **specifically watched** for life-threatening hypoglycemia, hypotension, and drug-drug interactions.

Hypoglycemia more often presents as **cognitive impairment** in the elderly, rather than tremulousness and sweats. Most likely causes of hypoglycemia are **insulins** and the **insulin secretagogues** (sulfonylureas and meglitinides), especially the 1st generation (chlorpropamide). Glyburide has about twice the incidence of hypoglycemia in the elderly compared to glipizide (27% vs. 14%) and is no longer recommended for use as a 1st line sulfonylurea by the American Diabetes Association (ADA).

Be cautious with **metformin** use in the elderly because of the high prevalence of renal insufficiency in this population and the tendency of these patients to develop lactic acidosis. Measure CrCl prior to use of metformin in

patients > age 80, and do **not** give the drug to any patient with a CrCl < 60, regardless of age.

Rosiglitazone is no longer recommended for use by the ADA. Pioglitazone also should be avoided in the elderly, due to the risk of edema and precipitation of CHF. The jury is still out, also, on whether these drugs are associated with an increased risk of cardiac events and stroke.

Remember to adjust downward the insulin doses as renal function declines with age, especially as GFR drops below 50 cc/min.

Hyperthyroidism

People > 60 years old with thyroid disease are more likely to have vague symptoms that could indicate either hyper- or hypothyroidism. Features of classic **hyperthyroidism**, such as hyperreflexia, heat intolerance, tremor, nervousness, polydipsia, and increased appetite, are usually absent in elderly persons. “Apathetic hyperthyroidism” can be seen in elderly patients and presents as apathy, fatigue, anorexia/weight loss, and tachycardia.

Atrial fibrillation and anorexia can occur in older patients with **hypothyroidism**; we rarely see these symptoms in hypothyroid younger patients.

Hormone Replacement Therapy (HRT)

Estrogen replacement is the best option for alleviating vasomotor and other menopausal symptoms and can be used safely for short periods.

The most substantial data we have on HRT are from the Women’s Health Initiative (WHI), published in 2002. Prior to this study, the standard of care (based on observational data) had been to prescribe HRT to postmenopausal women to protect their bones and prevent coronary disease. The WHI data, however, showed that HRT (estrogen only) is **ineffective** long term for preventing heart disease, and that combination HRT is associated with a slight **increased risk** for heart disease, stroke, venous thrombosis, and breast cancer. Both groups had an increased incidence of gall bladder disease. Combined therapy did reduce the risks of colon cancer and osteoporotic fractures, but not enough to justify these increased risks.

Follow-up analysis of the WHI data tells us that the women who experienced the heart disease and strokes were the older women in the study.

Conclusions from WHI that drive practice today:

- **Combination HRT** is associated with an increase in heart disease, stroke, venous clotting, breast cancer, and gall bladder disease. Unopposed estrogen use was not associated with the heart disease or breast cancer risks.
- Younger, perimenopausal women do not appear to have an increased risk for heart disease and stroke with combination HRT. But older women do.

Quick Quiz

- What is the typical presentation of Paget disease?
- What complications are geriatric patients specifically at risk for developing as they are being treated for diabetes?
- Metformin should not be given to patients with creatinine clearance below what calculation?
- What is apathetic hyperthyroidism?
- What are the main features of delirium? Precipitating factors?
- How is delirium different from “sundowning”?
- What is the recommended drug for elderly patients with delirium?
- How is dementia different from delirium?
- Estrogen alone causes endometrial hyperplasia and increases risk of endometrial cancer. Combination estrogen-progestin in women with a uterus is not associated with this risk.
- Premature ovarian failure (menopause before age 40) can be safely treated with combination HRT until the woman is 50 years old; then, stop and discuss the risks.

The important concept: Do **not** give women > 50 years old combination HRT because it increases their risks for stroke, heart disease, breast cancer, venous clotting, and gallstones—and the reduction in fractures is inadequate to compensate for these increased risks. Perimenopausal use of estrogen replacement is discussed later in Office Gynecology (see [page 10-56](#)).

NEUROLOGIC

Delirium

Delirium is confusion with altered consciousness. It is a common problem in the elderly. Main features are **abnormal** attention span (easily distracted), **disorganized** thinking (may have hallucinations), and **altered** consciousness (with increased or decreased mental activity) that fluctuates during the day and typically worsens at night. Patients with underlying dementia and/or stroke are at highest risk.

Common precipitating causes include drugs, poor nutritional status, acute illness (e.g., infections, volume depletion). Know that physical restraints and bladder catheters can incite delirium as well. In the post-op period, uncontrolled pain is a major cause, especially in geriatric patients with hip fractures.

1/3 of cases will be caused by drugs. Drugs to be aware of **especially** include meperidine, NSAIDs, any new antimicrobial, diphenhydramine, all cardiovascular

drugs and antidepressants, antiemetics, baclofen, H₂ receptor blockers, sleep-inducers, and herbals (e.g., St. John's Wort and valerian root). Acute discontinuation of alcohol, benzodiazepines (BDZs), SSRIs, and pain medications may cause **withdrawal** delirium.

Know that in the elderly, delirium may be the **only** manifestation of illness. Any patient who becomes delirious should be thoroughly evaluated for a serious precipitating cause.

Evaluate the confused patient with an objective tool such as the MMSE or the CAM (see [page 10-10](#)). Physical exam should focus on identifying an **underlying acute illness** that may be associated with confusion (e.g., drug abuse, hepatic failure, uremia, head injuries, stroke, and seizures). Work up the central nervous system (imaging and LP) if no cause is found after a thorough search.

Differentiate delirium from “sundowning”: Sundowning is a disturbance in behavior that occurs **predictably** in the evening among some patients who live in chronic care environments. It is **not** associated with a precipitating illness and is **not** delirium. With sundowning, usually the care facility can tell you that the patient predictably deteriorates at night.

Treatment of delirium is supportive with focus on diagnosis and treatment of the underlying cause. Calendars and orienting signs, night lights, newspapers, a radio, glasses, and hearing aids help stabilize and prevent decompensation. It is also necessary to minimize daily stress.

Pharmacologic treatment of delirium in the elderly is tough because the meds themselves can worsen the confusion. Low-dose haloperidol is still recommended for most patients, but watch for prolongation of the QT interval—and do **not** use it in patients with Parkinson's. Alternative drugs include the atypical antipsychotics: risperidone, olanzapine (Zyprexa®), and quetiapine (Seroquel®). These drugs are as effective with fewer side effects than full-dose haloperidol, but they are expensive. Don't use BDZs in delirious patients because they make patients more confused and drowsy.

Use of a “sitter” and other nonpharmacologic interventions are always the best first choices. Remember to avoid physical restraint of geriatric patients at all costs because it precipitates delirium and causes falls.

Dementia

Patients with dementia have a progressive deterioration of cognition that is insidious and chronic—but without altered consciousness, as with delirium. The deterioration can be either very gradual or step-wise (related to the underlying cause). The cognitive impairment presents as:

- Difficulty learning and remembering new information
- Decreased problem-solving of both simple and complex tasks

- Decline in spatial organization → they get lost
- Trouble with impulse control → unusual behavior

Some decline in cognition occurs with normal aging, but memory loss is mild and should not affect the patient's daily living or be especially noticeable by family.

Most patients in the U.S. with dementia are diagnosed with **Alzheimer** disease (80%), followed by **multi-infarct** dementia. Lewy body dementia and dementia from Parkinson's are less common syndromes. See the Neurology section, Book 5, for a more thorough discussion.

Depression can look like dementia, especially in the elderly. A couple of ways to tell the difference: Depressed patients often present complaining of memory loss, while demented patients are brought in by family or friends. Depressed patients have a depressed affect and slowing with completion of the MMSE or Mini-Cog, while demented patients have a more normal affect and try hard. Assessment tools can help identify the true cognitive defects of dementia. A score of < 24 points on the MMSE is consistent with dementia/delirium.

At this time, the position of the U.S. Preventive Services Task Force on screening for dementia is that there is insufficient evidence to recommend for or against it.

First-line treatment for Alzheimer's is the cholinesterase inhibitors (CIs): **donepezil** (Aricept®), **rivastigmine** (Exelon®), and **galantamine** (Razadyne®). Tacrine is associated with liver toxicity. Best results with CIs are achieved in **mild-moderate Alzheimer dementia**, but other causes of dementia (e.g., multi-infarct and Lewy bodies) sometimes also improve. CIs do not help patients with Huntington disease, however. CIs can be combined with memantine (Namenda®), which is an N-methyl-D-aspartate receptor antagonist.

CIs provide a small benefit and help some patients carry out their activities of daily living (ADLs). Data are conflicting on their long-term effects. Not every patient receives benefit, either. The combination of cholinesterase inhibitor plus memantine appears to be better than CI alone.

Vitamin E is no longer recommended as a supplement because it may increase the risk of heart disease and death. **Ginkgo biloba** extract and **vitamins A and D** have not been shown in clinical trials to improve cognition in elderly patients.

In March 2008, the ACP published dementia treatment guidelines. These guidelines were evidence-based and demonstrated little benefit for any of the current cholinesterase inhibitors or memantine; the authors recommended that individual patient factors would likely determine need to initiate therapy because the data were not very compelling for initiating therapy in any

patient. Know that the benefit from treating Alzheimer's is greatest **early** in the disease, and the cholinesterase inhibitors should be stopped in patients with severe dementia.

Depression

Depression is the **most common** mental problem in the elderly. It is particularly likely to occur in those who live in institutionalized settings and/or have chronic diseases, especially just after a severe sickness or in states of chronic pain. Know that the depressed elderly (especially men) make up 1/4 of the successful suicide attempts in the U.S.

Look for dysphoria, psychomotor slowing, anorexia, weight loss, and multiple "aches and pains." Know that insomnia is associated with depression, especially in the elderly, although it is not known whether it is a symptom or a cause. Depression-associated delusions are more common in the elderly than in the general population. Pay special attention to the elderly man with depressed mood, hopelessness, chronic pain, and insomnia because his suicide risk is particularly high.

A host of substances and drugs can potentiate depression, including alcohol, BDZs, opiates, and barbiturates. Untreated thyroid disease, diabetes, and pain are organic causes.

Treatment is usually psychotherapy combined with antidepressants +/- electroconvulsive therapy (ECT). **Exercise** helps, too. Selective serotonin reuptake inhibitors (SSRIs) are the 1st line drugs because they have fewer side effects than other choices. The most common reason for stopping these agents is sexual dysfunction! (See Table 10-8 on page 10-18.)

With antidepressants in the elderly, **always** start with low doses (typically 1/2 the normal dose) and increase **slowly** with the goal of eventually reaching the normal therapeutic dose. See patients (or call them) within 2 weeks after initiating meds. Watch for the side effects of **hyponatremia** and **tremor** in elderly patients on SSRIs. It takes about 8 weeks to see improvement; 6–12 months is the usual duration of treatment. Know that treating a patient's depression can help their comorbidities improve as well.

Sleep Disturbance

Insomnia

Sleep disturbance is a common problem in elderly persons, and normal aging is associated with more frequent awakenings. These disturbances include difficulty falling asleep (> 30 minutes), frequent awakenings, waking too early, and feeling generally unrestored. When the disturbance also causes problems for the patient during the day (e.g., poor concentration, moodiness, sleepiness, fatigue), it is classified as "insomnia."

Quick Quiz

- What are the 2 most common causes of dementia in the U.S.?
- When do patients derive the greatest benefit from Alzheimer treatment?
- What are common symptoms of geriatric depression? Side effects of meds?
- Name some medications typically associated with insomnia in the elderly.
- What is the role of benzodiazepines in treatment of insomnia?
- What dangerous side effects are sometimes seen with both benzodiazepine and non-benzodiazepine sleep agents?
- What is a common condition associated with restless leg syndrome?

Know what is **not** insomnia:

- Some people can sleep well for only a few hours and have no problem functioning the next day. These patients simply have short-duration sleep.
- People who have not slept voluntarily (because of work or whatever) and can easily fall asleep during the day are classified as having “insufficient sleep” or “sleep deprivation,” not insomnia.

Insomnia, especially in the elderly, is associated with worsening of hypertension, heart disease, lung disease, urinary incontinence, chronic pain, and depression.

History should focus on characterizing the sleep disturbance (sleep logs help) and identifying any untreated comorbidities and/or precipitants (e.g., naps, stress, newly stopped or started meds, alcohol, caffeine, nicotine).

Medications specifically associated with insomnia include corticosteroids, beta-blockers, beta-agonists, and stopping sedatives or pain meds.

Labs are recommended only to diagnose potential comorbidities (e.g., hyperthyroidism, restless legs). Sleep studies are unnecessary until a patient has failed to respond to conservative management.

Treatment should be directed at improving any poorly managed comorbidities, and advise the patient on good sleep hygiene:

- Set a schedule for sleep and stick to it.
- Get in the bed only when you're sleepy. When you're rested, get up.
- Minimize excess light and sound in the bedroom.
- Exercise during the day, at least 4 hours before bedtime.

- Stay away from caffeine, nicotine, and alcohol near bedtime.
- Eat dinner or an evening snack to prevent bedtime hunger.
- Don't fight sleep. If you can't sleep for > 20 minutes, get up and do something relaxing (reading or music). No bright lights or TV.

The most efficacious treatment in patients with uncomplicated insomnia is **behavioral**—not pharmacologic. Elderly patients are especially susceptible to bad outcomes from sleep drugs.

Benzodiazepines (BDZs) actually do help by decreasing the frequency of awakenings, reducing time to fall asleep, and increasing duration of sleep. But they have many negative side effects, including addiction, loss of memory, and accumulation of metabolites.

Non-benzodiazepine insomnia drugs, such as zolpidem (Ambien®), zaleplon (Sonata®), and eszopiclone (Lunesta®) have more selective effects than BDZs because they affect only a portion of the receptor subunits that BDZs affect. Because of this, non-BDZs tend to have more sedative than anxiolytic effects than BDZs. Additionally, they don't have as many side effects as BDZs.

Even so, both BDZs and non-BDZs can cause confusion, wandering, imbalance, and daytime grogginess in the **elderly**—hence both classes are **avoided** in geriatric patients.

Many sleep-aid drugs in both the BDZ and non-BDZ classes have received FDA-required label changes, indicating that the drugs can cause a hypnotic state that allows patients to attempt complex tasks while sleeping → bizarre behaviors (e.g., having sexual intercourse while not apparently awake, erratic driving, making incoherent phone calls).

The melatonin agonist, **ramelteon** (Rozerem®), does seem to improve sleep for some patients, and the drug is not associated with any known untoward effects. It is a **good choice** for the elderly, albeit with variable efficacy.

Stay away from older antidepressants (e.g., amitriptyline), diphenhydramine, haloperidol, and barbiturates in most patients (because of side effects) but especially in the elderly.

Restless Leg Syndrome (RLS)

Restless leg syndrome is a common sleep disorder in the elderly (prevalence = 20% in age > 80 years). The hallmark of RLS is leg discomfort +/- paresthesias at rest, relieved immediately with movement. Usually, pain is “deep seated” and localizes below the knees. Symptoms are worse in the evening and at night.

RLS can be primary or caused by other conditions: **iron deficiency** (even without anemia), dialysis, diabetic neuropathy, multiple sclerosis, Parkinson's, pregnancy, and

Table 10-8: Antidepressants, Selective Receptor Blockers

Drug	T 1/2 (hrs)	Mechanism of Action/Blocks ...	Notes	Drug of Choice for ...	Caution (!) in patients ...
Fluoxetine (Prozac®, Serafem®)*	72	SSRI	May cause anxiety and insomnia		... with insomnia
Paroxetine (Paxil®, Pexeva®)*	20	SSRI	Most anticholinergic of the SSRIs Sedating in some		... in whom anticholinergics are to be avoided. ... with insomnia
Sertraline (Zoloft®)*	25	SSRI	GI discomfort is common		... with insomnia ... with irritable bowel
Fluvoxamine (Luvox®)*	15	SSRI	Most sedating of the SSRIs	... pts with agitation ... pts with insomnia ... pts with obsessive-compulsive disorder	... with irritable bowel
Citalopram (Celexa®)*	35	SSRI	May cause anxiety and insomnia, N/V, headache		
Nefazodone (Serzone®)	3***	SSRI and 5-HT ₂ and has anti-alpha adrenergic activity	Maintains sleep architecture Sexual dysfunction is unlikely	... pts with insomnia; ... to maintain sexual activity	... on benzodiazepines or antihistamines (interacts with cytochrome P-450 system)**
Venlafaxine (Effexor®)	4	SSRI and norepinephrine reuptake and some dopamine reuptake			... with insomnia ... with HTN —usually increases blood pressure, so not used in these patients
Bupropion (Wellbutrin®)	15	Reuptake of dopamine and some norepinephrine	Sedation is unlikely Sexual dysfunction is unlikely		... with insomnia ... with HTN —may increase blood pressure
Mirtazapine (Remeron®)	20	Presynaptic alpha ₂ receptor (increases serotonin and norepi release) AND 5-HT ₂ AND 5-HT ₃	Agitation is unlikely Sexual dysfunction is unlikely Good for insomniacs	... pts with insomnia; ... to maintain sexual activity	Most anticholinergic of all these ... with HTN —may increase blood pressure

*All the SSRIs have a tendency to cause agitation, sedation, and sexual dysfunction. Pure SSRIs are **not** likely to increase blood pressure.

**May use loratadine (Claritin®) or lorazepam (Ativan®) with nefazodone.

***T 1/2 is higher than this in elderly, especially women.

Note 1: **Buspirone** is a 5-HT_{1A} agonist that can be combined with an SSRI to decrease the dose or improve efficacy.

Note 2: Any SSRI may cause an increase of suicidal thought or actions in 1 of 50 age < 18 years.

others. Make sure that the patient's complaints aren't actually akathisia from medications (phenothiazines and SSRIs).

Diagnosis is made based on clinical history, a normal neuro exam, and absence of kidney disease. Always check a ferritin level to rule out iron deficiency even if the patient does not have anemia.

The following expert panel recommendations are based on whether the RLS is intermittent, daily, or refractory.

- **Intermittent:** Try nonpharmacologic therapy first: iron-replacement therapy; mental alerting activities (such as video games or crosswords); avoidance of caffeine, nicotine, and alcohol.
Then, if needed, try one of the following:
 - Dopamine agonists generally are the drugs of choice: pramipexole, ropinirole.
 - Levodopa. Be careful—may cause augmentation (worsened symptoms or rebound).
 - Benzodiazepines (generally avoided).
 - Low-potency opioids (generally avoided).

Quick Quiz

- What cause of dizziness is associated with improvement when the patient holds onto a walker?
- Which maneuver helps identify benign positional vertigo?
- **Daily:** Try nonpharmacologic first, then dopamine agonists, gabapentin, and, lastly, low-potency opioids.
- **Refractory** to dopamine agonists: Try gabapentin, a different dopamine agonist, combination therapy, then tramadol and, lastly, high-potency opioids.

Dizziness

Dizziness is common in the elderly but is not a normal consequence of aging. When any patient complains of “dizziness,” take a good history (more sensitive in making the diagnosis than PE, labs, or studies) to determine which of the following she is actually describing:

- Vertigo: “spinning,” “whirling,” or “moving” of either her or the environment that is worse with head movement and occurs in spells (days to weeks), then eventually resolves.
- Nonspecific dizziness: unable to characterize better; sometimes “lightheaded” is used to describe.
- Disequilibrium: imbalance with standing and walking, especially with turning.
- Presyncope: almost “fainting” or “blacking out” while either standing or seated (not supine), possibly associated with sweating, a sensation of warming, visual blurriness, and nausea.

A complete discussion about the workup of dizziness is included in the Neurology section, Book 5. Multisensory deficits causing disequilibrium and benign positional vertigo are common. In geriatric patients, the cause is more often vestibular than in other patient groups.

The common causes of dizziness in the elderly usually can be discovered by history.

Presyncope. Dizziness that sounds like presyncope or “faintness” should be taken seriously and evaluated with a cardiovascular workup, especially if the patient has known heart disease, palpitations, or a history of true syncope.

Multisensory deficits. Think about multisensory deficits as a cause for disequilibrium in the patient with a mix of visual, hearing, orthopedic, and neuropathic impairments (sometimes also called “benign dysequilibrium of aging”). He complains of “feeling unsteady” and improves with a walker or when someone holds his arm. Treat this by maximizing support for each sensory impairment and providing assistance devices (e.g., canes, walkers).

Benign positional vertigo (BPV) presents as recurrent (lasts for weeks in spells), short-lived (< 1 minute), with episodes of vertigo that predominantly occur when the patient changes position. The vertigo can be bad enough to cause nausea and vomiting; but, otherwise, the patient has no other symptoms (e.g., hearing loss, headaches). Know that BPV occurs more often in geriatric patients who have giant cell arteritis (see the Rheumatology section, Book 3). So, take a good history in the dizzy elderly patient to determine whether symptoms of vasculitis or polymyalgia rheumatica are also present (e.g., weight loss, fevers, musculoskeletal pain).

In uncertain cases, BPV can be diagnosed by performing a maneuver in the office called the Dix-Hallpike test. This test turns the patient’s head, then rapidly tilts her backwards for 30 seconds, then upright again, with subsequent observation for nystagmus. Repeat the maneuver with the head turned in the opposite direction. Visible nystagmus in either the recumbent or the upright position signals a positive test.

In these cases, the differential diagnosis includes central causes of vertigo such as cerebellar lesions (strokes or masses); so if the history is suggestive, do further workup with imaging and electronystagmography (water calorics).

Treatment of BPV can be accomplished through one of 2 office maneuvers, Epley and Semont, both equivalent in efficacy and designed to reposition the floating debris felt to be responsible for the vertigo. The maneuvers are variants of the Dix-Hallpike test, where you lean the patient backwards and forwards with an associated neck tilt. Alternatively, exercises can be prescribed for home that aim to have the same result (but are less effective). No drugs are used to treat BPV.

HEARING

Decreased hearing is an age-related condition. About 1/3 of patients > 65 years of age have hearing loss. The most common cause is presbycusis, which is just age-related sensorineural hearing loss. It is bilateral, and loss of higher frequency sounds is more common. Be sure to check for cerumen impaction. See other causes of decreased hearing on page 10-47. Hearing aids can help these patients.

CARDIOVASCULAR

Walking more than 4 hours per week is associated with a dramatic decrease in cardiovascular-related hospitalizations in persons > 65 years of age.

Isolated systolic hypertension is a common finding in elderly patients. It increases the risk of myocardial infarction and stroke 2–4x. Several studies show these patients benefit from treatment, so long as the diastolic pressure doesn’t fall too low (< 60 mmHg).

In the elderly, start with about 1/2 the standard dose of any one of the following: thiazides (chlorthalidone is

now being favored over hydrochlorothiazide because of its superior efficacy and reduced rate of hypokalemia), dihydropyridine calcium channel blockers (e.g., amlodipine), or ACE inhibitors/angiotensin II receptor blockers. **Avoid beta-blockers** for treatment of systolic hypertension in the **elderly** because they don't work as well as the other treatments and have been associated with increased mortality.

The 6-month mortality rate after an MI increases with age—from 4% around age 66 to 12% when older than 80 years. (Group = first MI, with thrombolytics, discharged from hospital.) Only about 75% of eligible patients are receiving aspirin on discharge from the hospital. Be sure to prescribe an antiplatelet drug to these patients!

CHF. The incidence of congestive heart failure (CHF) in the elderly is increasing dramatically and is now the **number 1 cause of hospitalizations** in this group. (Number 2 is pneumonia.)

Treat CHF itself primarily with diet, diuretics, and ACE inhibitors. Digoxin is indicated only for more severe heart failure. Isosorbide dinitrate and beta-blockers have an important **secondary** role. Use of NSAIDs is an important precipitant of CHF in older patients who already have risk factors for CHF.

Mortality benefit has been shown for ACE inhibitors, beta-blockers, and spironolactone. If you use spironolactone, follow K^+ closely. Spironolactone benefit has been shown in patients with class 4 CHF or class 3 with a history of class 4.

PULMONARY

Geriatric Asthma

Elderly patients with asthma may have long-standing asthma acquired in childhood/young adulthood, or they may have developed it as an aging adult. Around 8% of adults > age 65 are diagnosed with adult-onset asthma. Be aware that it is commonly misdiagnosed as COPD because COPD is more likely to occur in this age group.

Risks for development of adult-onset asthma are the same as for younger patients: allergens and irritants (e.g., tobacco smoke, occupational vapors, air pollution). **Comorbidities** are important, especially coronary heart disease, because treatment of asthma with beta-agonists can cause myocardial ischemia. Also, beta-blockers used as antihypertensive drugs can **exacerbate** airway obstruction.

Asthma in the older patient can present the same as in the younger patient, although the elderly tend to have **fewer symptoms** with the same amount of disease. Specifically, they complain less of dyspnea associated with obstruction and wheezing—likely due to their reduced activity, they fail to notice they are short of breath. Definitive diagnosis is made with **spirometry**, when the FEV_1 and FEV_1/FVC are reduced. In the elderly, the traditional cutoff of 70% for a diagnosis of

obstruction, as recommended by the GOLD group (see the Pulmonary Medicine section on Asthma, Book 2), is **not** used. This is due to the fact that this criterion is not as specific in this age group and will **overdiagnose** asthma! Instead, for diagnosis of asthma in the elderly, most experts use an $FEV_1/FVC < 89\%$ of the **lower limit of normal for age**. A response to bronchodilators is still expected, as per the GOLD criteria, for diagnosis: > 200 cc increase in FEV_1 post-bronchodilator and > 12% of predicted.

Separating COPD from asthma is important, especially in the elderly where rates of COPD are high. Know that reversible obstruction is consistent with asthma, and a low DLCO is consistent with emphysematous COPD.

Bronchoprovocation is used to diagnose asthma in patients with normal spirometry, the same way as it is used in younger people.

Management of geriatric asthma is the same as for younger patients, but theophylline is **not** recommended, even as an alternative drug, because of the significant potential for toxicity.

Geriatric Sleep Apnea

Think about sleep apnea as a potential cause of reduced cognition in geriatric patients. Know that apnea which results in poor sleep and excessive daytime somnolence carries a higher rate of morbidity in patients who are frail and already prone to falls. Diagnosis and management is the same as in younger patients.

UROLOGY

Urinary Incontinence

Overview

Normal micturition is dependent on an intact neurologic pathway from the brainstem to the bladder, which causes relaxation of the sphincter muscle's tonic contractile state just milliseconds before contraction of the detrusor (bladder muscle). Additionally, voluntary control of micturition requires communication between the cerebral cortex and the brainstem.

Urinary incontinence, although a common geriatric problem, is **always** considered a pathologic condition that is not a normal consequence of aging! Always consider the possibility that the patient has a serious underlying condition responsible for the leakage.

Normal, age-related changes to the urinary tract include **decreased** flow rate, decreased bladder capacity, and **increased** residual volume. As a function of these changes, it is normal for patients to get up once during the night to void.

Urinary incontinence may be thought of as either a "storage problem" or an "outflow" problem. Storage problems are "detrusor" or bladder over- and under-contraction, while outflow problems are outlet obstruction or incompetence.

Quick Quiz

- What are the GOLD recommendations for diagnosis of asthma in the elderly?
- Is urinary incontinence considered a normal consequence of aging?
- What are the 4 types of incontinence?
- What is the best treatment for urge incontinence?
- What is the best initial treatment for stress urinary incontinence?

There are 4 general, symptom-based types of urinary incontinence:

- 1) **Urge** = Leakage (a lot or a little) associated with the feeling of urgency
- 2) **Stress** = Leakage associated with increased intraabdominal pressure (e.g., coughing, sneezing)
- 3) **Mixed** = Leakage associated with both an urgency and increased intraabdominal pressure
- 4) **Incomplete Bladder Emptying** = Leakage (a lot or a little) after voiding

Note that “overactive bladder” is not necessarily incontinence. It is a urologic condition defined by the urgent need to void frequently and during the middle of the night. Occasionally, the urgency may be associated with leakage, in which case it is called urge incontinence (next).

Urge Incontinence

Urge incontinence (UI) is a **common** cause of geriatric incontinence. With urge incontinence, there is passage of **either small or large amounts** of urine, associated with a sense of urgency often set off by a precipitating stimulus: hearing running water, unlocking the door to the house, entering cold environments.

UI is related to overactive bladder.

UI and overactive bladders are caused by uncontrollable bladder contractions (“**detrusor instability**”)—usually caused by **CNS problems** (termed “detrusor **hyperreflexia**”), but also sometimes a result of **cystitis**.

Detrusor hyperreflexia is due to progressive loss of communication between the frontal lobes and the micturition center in the brainstem. As the bladder loses the modulating influence from the brain, it tends to spasm more often.

Treatment is best accomplished with **behavioral therapy**, called bladder training. When an urge to void becomes profound, the patient is instructed to attempt relaxation techniques that help the urge subside and allows short-term voiding delay. Once the urge is controlled, the

patient can walk calmly to the restroom and urinate. The goal is to eventually delay voiding to every 4 hours with no interval leakage.

Bladder training is more effective than the more commonly prescribed therapy of antimuscarinic agents (oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, darifenacin, hyoscyamine, and tricyclic antidepressants), all of which are equivalent in efficacy and relax the bladder muscle. They have other **anticholinergic** side effects (e.g., dry mouth, tachycardia, constipation). Even so, these antimuscarinic agents are helpful when used as an **adjunct** to bladder training—short term, as needed. Remember that anticholinergics can precipitate acute angle glaucoma! Also, do **not** use them for incontinence in patients who are taking cholinesterase inhibitors for dementia because the combination **accelerates** cognitive decline.

Pelvic muscle exercises (Kegel’s) are also helpful for UI.

Stress Incontinence

Stress urinary incontinence (SUI) is second in frequency in geriatric **women**. With SUI, the urethra cannot maintain the pressure gradient required for urinary control when there is an increase in intraabdominal pressure (cough, jumping, etc.). SUI is associated with multiple vaginal deliveries, pelvic surgery, postmenopausal hormonal changes (low estrogen → atrophic relaxation of the vaginal wall → lack of support for the urethra) but is sometimes seen in males post-prostatectomy. Stress incontinence is initially best treated with behavioral therapy, especially **Kegel exercises** (perineal muscle contractions); referral to a pelvic floor physical therapy specialist can be helpful in effective teaching of Kegel’s. Note that some women with urinary incontinence have a mixture of SUI **and** urge incontinence. Surgery has high cure rates but with high risk of complications. Periurethral collagen injections are an option for those who cannot have (or don’t want) surgery and who do not improve with exercises.

The **history** gives you the clues to determine whether incontinence is due to urge or stress incontinence—look for the stimuli that precipitate leakage in a patient with UI and look for leakage associated with increased intraabdominal pressure with SUI.

Mixed Incontinence

Mixed incontinence, again, is a combination of urge and stress incontinence. The true etiology is unknown. Bladder training and Kegel’s help these patients, too.

Incomplete Emptying

Incomplete bladder emptying is sometimes still called “overflow incontinence.” It is caused by either an overactive bladder +/- an outlet obstruction **or** by an underactive bladder that has trouble contracting (e.g., diabetes, Parkinson’s, alcohol abuse).

Although rare in females, incomplete emptying in males is usually caused by prostatic hypertrophy. **The outlet obstruction** causes a distended bladder and high-volume, post-void retention. Anticholinergic drugs are the most common causes of drug-induced incomplete emptying. Psychogenic retention can also be a cause.

Most types of incomplete emptying do indeed cause urgency and may be seen as a type of urge incontinence.

Treatment includes alpha-blockers for men with benign prostatic hypertrophy (BPH).

Review

- Bladder training and Kegel exercises: urge, stress, and mixed.
- Drugs for urge and mixed (anticholinergics with antimuscarinic effects): oxybutynin, tolterodine, trospium, solifenacin, darifenacin.
- Drugs for stress: None! Bladder training and Kegel's only!
- Surgery: last resort for stress.
- Incomplete emptying: Treat underlying cause if possible; intermittent catheterization; "diaper-like" garments.

Know that asymptomatic bacteriuria, while common in the elderly, is **not** a cause of incontinence. Also know that incontinence is **never** an indication for a long-term bladder catheter.

Fecal Incontinence

Geriatric fecal incontinence is usually caused by fecal impaction and secondary overflow incontinence. The impaction is usually a result of lax muscles and neuronal degeneration. Typical presentation is an elderly person with complaints of diarrhea and abdominal discomfort and who has hard stool in the rectal vault on physical exam. Treatment is disimpaction and subsequent bulking agents.

Benign Prostatic Hyperplasia (BPH)

The prevalence of benign prostatic hyperplasia (BPH) increases from about 10% at age 30 to **> 80% at age 85**; about 15% of these patients have impaired urination. We still don't understand what causes BPH and have yet to identify any specific risk factors—except **age**. BPH does **not** increase the chance of prostate cancer.

Symptoms of BPH are fairly specific for urinary retention: frequency, hesitancy, difficulty starting and stopping the stream, urgency, and nocturia. Certainly other diseases can cause these symptoms (e.g., bladder cancer, cystitis) and should be considered before making a diagnosis of BPH.

The **2 definitive tests** that should be done: 1) a digital rectal exam to palpate the prostate and assess for irregularities and increased size and 2) a urinalysis to assess

for hematuria (with a culture if infection is suspected). Know that serum prostate-specific antigen (PSA) levels increase as the prostate increases in size, so PSA screening for prostate cancer is **less** specific in men with BPH (more false positives).

BPH is treated only if it significantly affects the patient adversely and/or if it is associated with outlet obstruction, causing hydronephrosis or acute kidney injury.

Treatment starts with medical therapy: **alpha-blockers** (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin) or **5-alpha-reductase inhibitors** (finasteride, dutasteride).

Recommended treatment of symptomatic patients starts with behavioral therapy. Medical therapy generally starts with the alpha-blockers alone and then, if needed, 5-alpha-reductase is added later.

Note: Of the alpha-blockers, prazosin is **not** used for BPH because it requires frequent doses and has more side effects.

Most common side effects of these meds are **orthostasis and dizziness**. Be careful with combining sildenafil or vardenafil with these drugs because the combination worsens hypotension.

The 5-alpha-reductase inhibitors, which reduce circulating testosterone, take at least **6 months** to decrease prostate size and relieve symptoms. These drugs work better for large prostates and have a more durable effect. The major side effect is impairment of sexual function (decreased libido and delayed ejaculation). Know that these drugs **decrease serum PSA**, even in cancer patients, so recommendations are to multiply the measured PSA by 2–2.5, depending on how long the patient has been taking the drug.

Transurethral resection of the prostate (TURP) is now the treatment of last resort, used when drugs fail to work.

Other guidance: Make sure patients know to reduce intake of caffeine and alcohol (diuretics), stay away from fluids before bed, and attempt to urinate twice to completely empty the bladder.

Erectile Dysfunction (Impotence)

Overview

The most common type of male sexual dysfunction is **erectile dysfunction (ED)**, which is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse. It is not uncommon for men to experience brief episodes of ED. "Impotence" is the term reserved for ED that occurs in **> 75%** of sexual encounters.

The smooth muscle in the flaccid penis is in a state of tonus or contraction due to **alpha stimulation** by norepinephrine. **cGMP** is made, along with **cAMP**—made by the norepinephrine and vasoactive intestinal peptide (VIP) pathways. This cGMP causes the relaxation of the smooth muscle in the penis, which increases the inflow through the helicine artery into the erectile

Quick Quiz

- What is a common cause for incomplete bladder emptying in males?
- What is the role of bladder catheterization in the treatment of geriatric incontinence?
- How does prostatic hyperplasia affect PSA levels?
- What is the initial treatment for BPH?
- What is the most common cause of neurogenic ED?
- Which medications most commonly cause erectile dysfunction?
- If an exam presents a young male with erectile dysfunction who is on no medications, what is the most likely etiology?
- What is the mechanism of action for sildenafil?

tissue. The swelling of this tissue causes compression of the outflow venules, resulting in a sustained erection.

ED can be caused by **organic** or **psychological** problems, or as a side effect of medications (25% of cases!). Most causes of ED are at least partially organic. The organic causes are neurogenic, vascular, hormonal, and normal aging.

Classic Presentations and Causes of ED

There are many causes of ED. These can be grouped as follows:

- **Organic causes:** Usually **slow** onset. Loss of nocturnal and morning erections.
 - **Neurogenic:** Usual cause is **diabetes**. Other causes are surgical procedures (especially prostate), MS, ALS, Parkinson's, and other causes of peripheral neuropathy. Cyclists who spend > 3 hours/week on an upright bicycle can experience ED due to pressure that the seat places on the pudendal nerves (reducing blood flow to cavernosal artery).
 - **Vascular:** Usual cause is diabetes and/or cardiovascular disease. Other causes are surgical procedures, inflammatory conditions, or pelvic fracture. In elderly men, ED is caused by vascular compromise in 50% (indicated by a low penile brachial pressure index [PBPI]). ED due to vascular compromise indicates increased risk of present and future major vascular disease.
 - **Hormonal:** often accompanied by a loss of libido. Symptoms may include gradual onset of frontal headaches or visual disturbances (space-occupying tumor); hot flashes and decreased need for shaving (decreased androgens); fatigue + weight gain + dry skin + constipation (hypothyroidism).

- **Normal aging:** Sexual potency **does** decrease with age.
- **Medications:** Especially antidepressants (SSRIs), clonidine, spironolactone, beta-blockers, and thiazide diuretics. Many others also cause ED, but these are some of the most commonly prescribed meds in the geriatric population.
- **Psychogenic:** Usually **acute** onset. This is the usual cause for ED in younger patients. They continue to have nocturnal and morning erections, but libido is lost. ED is directly correlated with depression. Unfortunately, SSRIs are associated with a very high incidence of sexual dysfunction (usually delayed ejaculation).

Treatment Options for ED

First-line treatment for ED [Know]:

Sildenafil citrate (Viagra®) inhibits phosphodiesterase type 5 (PDE5), an enzyme that inactivates cGMP. It works very well for many causes of ED. Side effects are due to its **vasodilatory properties**—headaches, flushing, dyspepsia, bluish hue in the vision. Reports of hearing loss have also been documented.

Vardenafil (Levitra®, Staxyn®) is similar to sildenafil in mechanism, effectiveness, and side effects.

Tadalafil (Cialis®) has the same mechanism of action as sildenafil and vardenafil but with a longer half-life. Erectile function may be improved for up to 36 hours. This drug is approved for daily use. One specific side effect is **back pain**.

Avanafil (Stendra™) is the newest agent (approved 2012) and is similar to the others.

PDE5 inhibitors are more likely to cause hypotension when taken with non-selective alpha blockers (prazosin, doxazosin, and terazosin). Uroselective alpha blockers (tamsulosin and alfuzosin) are less likely to cause hypotension. There is a risk of hearing loss with **all** of the PDE5 inhibitors. Contraindications are any concurrent nitrates. Relative contraindications are CHF, hypotension, unstable angina, HCM, and severe aortic stenosis.

Vacuum devices work well but are clumsy to use. They are indicated only when oral therapy is contraindicated or the patient prefers them to oral therapy.

Yohimbine is a naturally occurring alpha-blocker. It has minimal effect, but, because it is inexpensive and has minimal side effects, it is often tried on patients with a mostly **psychogenic** etiology. Better than placebo but much less effective than sildenafil.

Second-line treatment for ED:

Alprostadil (prostaglandin E1) injected into the corpora cavernosa of the penis works well. It is especially useful in patients with ED due to neurologic dysfunction.

Third-line treatment:

Penile implants. Various types—hydraulic, semirigid, and flexible rods. Usually used only for those who have

failed all other therapy. Complications are associated with the surgery. There is a risk of postsurgical infection. Scarring may cause erections to curve. Tissue erosion may occur. If there are no complications, they are effective and patient satisfaction rates are high.

ETHICS

OVERVIEW

Read the ACP's Ethics Manual, 6th edition (released 2012), available online at http://www.annals.org/content/156/1_Part_2/73.full

PHYSICIAN'S DUTY AND PATIENT'S RIGHTS

The physician's duty to the patient is based on 3 principles that are the basis for **all** ethical physician-patient interaction:

- 1) Beneficence—the duty to act in the best interests and welfare of the patient and the health of society
- 2) Nonmaleficence—the duty to do no harm to the patient
- 3) Respect for the patient's autonomy—helping the patient make free, non-coerced choices

Let's look at specifics.

The patient's right to accept or refuse health care is based on another 3 principles:

- 1) The philosophical concept of **personal autonomy**—a value held close to the heart in our culture
- 2) Personal liberty interest under the Constitution
- 3) Common law right of self-determination

Patients should be able to choose and follow their own ideas and plans for their life. Constraint of a person's free choices is permissible **only** when these choices infringe on another person's rights and welfare. **Paternalism**, the practice of overriding or ignoring preferences of patients in order to benefit them, used to be the standard of interaction between the physician and patient. Today, except for certain cases (mental illness and some emergencies), paternalism is considered ethically improper. Patients should be an active part of the decision-making process. Patients require informed consent, which is defined as the willing acceptance of medical intervention—after **adequate disclosure** by the physician—of the nature of the intervention and all of its risks and benefits.

Patients are entitled to disclosure of the following:

- The patient's current medical status with the probable course, whether or not medical intervention is used
- The medical interventions that may help and the risks associated with them
- The physician's opinion about other alternatives

- The physician's own recommendations based on best clinical judgment

Know that physicians are responsible for caring for patients with contagious infectious diseases. It is deemed unethical by ACP for internists to refuse care for patients with HIV/AIDS, hepatitis viruses, multidrug-resistant TB, and influenza because of a physician's own fear of becoming infected. It is assumed that the physician will take appropriate infection control precautions.

Know that physicians are responsible for providing honest information on disability claim forms and should not attempt to erroneously assist a patient in obtaining disability.

Generally, physicians should **avoid** caring for close family members and friends.

It is **absolutely unethical** for physicians to have any sexual relationship with a current patient, regardless of who initiates the relationship. The ethics document from the Federation of State Medical Boards says that physicians cannot even have sexual relationships with the **relatives** of existing patients.

Even former patients can cause ethical problems. The ACP ethics document says that physicians should “consult with a colleague or other professional before becoming sexually involved with a former patient.”

DISCONTINUING PATIENT RELATIONSHIPS

Physicians can sever relationships with patients so long as care is available by another physician (anywhere else), and the patient's health is not sacrificed. The physician must give the patient written notice of intent and must request approval from the patient for transfer of her medical records to the accepting physician. If this process is not followed, legal action can be taken for physician “abandonment.”

MEDICAL RECORDS

The physical chart belongs to the hospital or physician, but the information in the chart belongs to the patient. If requested, you must release the entire chart to the patient, and you cannot hold the chart hostage in exchange for payment of services. However, it is legal to charge a reasonable fee for copies.

ADVANCED DIRECTIVE

The advanced directive is the means patients have for stating which treatments they would accept or decline if they lost decision-making capacity. The advanced directive may also specify general goals for medical care and the patient's choice of a surrogate—a person with durable power of attorney for the patient's health care.

Quick Quiz

- Name a scenario in which a physician can ethically have a sexual relationship with a patient.
- What is the difference between an advanced directive and a living will?
- 6 months ago, Mr. Jones, a man with terminal cancer, decided to invoke a living will that said he refuses all life support in case of cardiopulmonary arrest. Today, he presents to the ED in severe distress and says he wants everything done, including intubation. His family doesn't want anything done, and you have the signed living will at the bedside. What should you do now that his personal preference has changed in the face of a signed living will and family wishes for nothing to be done?

A **living will** is a more focused form of advanced directive, in which the patient, for example, refuses life support when in a terminal condition. A lawyer is not needed to make a living will.

The patient has a right to change his/her mind! “Joe” has a living will. If he comes into the Emergency Department and requires intubation to survive—and states that he has changed his mind and wants all possible treatments available—then you honor his current decision.

Know that fluids and nutrition are ethically regarded as the **same** as other forms of treatment, and patients can address the desire for discontinuation of fluids and nutrition in their advanced directives.

PATIENT'S COMPETENCY OR DECISION-MAKING CAPACITY

The decision-making capacity refers to the ability to comprehend, evaluate, and choose among realistic options. The decision-making capacity of the patient can be difficult to determine. There are many transitory or reversible conditions that can interfere with this capacity. Examples are anxiety, depression, drug-induced confusion, and abnormal metabolic states. The waxing and waning associated with certain conditions, such as organic brain syndrome, is a manifestation of pathology, and the patient should be considered to have impaired capacity.

SURROGATE

A “surrogate” or “proxy” is a person who is authorized to make decisions on behalf of an incapacitated person. Traditionally, the next of kin has been considered the natural surrogate. In some states, there is a well-defined list of the order of next of kin, with priority given to natural surrogates—e.g., spouse, then parents, then children, then siblings. Another option is for the subject to give

someone durable power of attorney. This means giving decision-making authorization to a person who supersedes family members. **Remember:** The “contract for health care” is between the physician and **the patient**, not the patient's family.

The surrogate's decisions must promote the patient's wishes and welfare. If the patient has expressed certain wishes on a topic regarding medical intervention in the past, the surrogate **must** use that knowledge in the decision-making process. If the surrogate has no knowledge of the patient's wishes, then the surrogate must make decisions based on the patient's welfare. Welfare should include consideration of suffering, preservation of life, restoration of function, and quality of life; decisions should be based on what a reasonable person would want in similar circumstances. The surrogate's authority ends when the patient dies (i.e., they are not able to give consent for autopsy). Organ donation decisions should be broached at the appropriate time with decision makers by organ procurement specialists who are separate from prospective donors' health care providers in order to avoid conflicts of interest or a perception of conflicts of interest. Health care providers of prospective recipients should not be providing care to prospective donors for similar reasons.

EMERGENCY SITUATIONS

For patients unable to express their preferences, the physician may perform life-sustaining emergency procedures under the presumption that the alternative would be death or severe disability. All states have statutes allowing the physician to hold patients with certain psychiatric conditions against their will for medical and/or psychiatric treatment. This is often called a “medical hold.”

QUALITY OF LIFE AND PAIN RELIEF IN PALLIATIVE CARE

The quality of life in terminally ill patients in pain is considerably improved by proper pain relief. Terminal patients in pain are in a special situation, and their requests for pain meds generally should be honored. The downside of pain medications is that they can cause confusion and a decreased ability to communicate. You have to strike a balance between maximum pain relief and minimal decrease in consciousness. The assistance of hospice workers in this situation can be very helpful.

PHYSICIAN ERROR

Physicians must disclose to the patient **any** errors in judgment and procedure when the information is deemed “material to the patient's well-being.” In general, you always disclose errors—disclosure is **not** equivalent to admitting neglect.

PHYSICIAN-ASSISTED SUICIDE AND EUTHANASIA

Physician-assisted suicide is when the physician supplies the means of death to a patient, such as a prescription for a medication along with what is a lethal dose. Euthanasia is when the physician directly administers a lethal dose of a medication with the intention of causing death.

The latest guidelines by the ACP and the AMA do not support any form of physician assistance with suicide nor euthanasia.

Know that a patient refusing life-sustaining treatment is different from this.

Good end-of-life care entails treatment based on many issues. For instance, the ACP Ethics manual says that, when providing comfort to a dying patient, "...the physician may appropriately increase medication to relieve pain, even if this action inadvertently shortens life."

CPR AND DNR

Cardiopulmonary resuscitation (CPR) is usually a standing order in a hospital; i.e., it is to be carried out, without specific order, on any patient who suffers cardiac or respiratory arrest. The **only** time CPR is not done is when there is an order stating such—a "do not resuscitate" (DNR) or "do not attempt resuscitation" (DNAR) or "no code" order. The decision about non-resuscitation has 3 considerations that must be assessed:

- 1) Whether or not CPR would be futile; i.e., that the resuscitation would be unlikely to succeed or, if it did, another cardiac or respiratory arrest would soon follow.
- 2) The preferences of the patient.
- 3) Expected quality of life of the patient if resuscitation succeeds. It is the responsibility of the physician to initiate discussions with the patient (or, if the patient is incompetent, with family members or a surrogate) who is terminally ill or has an incurable disease with an estimated 50% survival of less than 3 years. The attending physician should clearly write the "do not resuscitate" order on the order sheet in the patient's chart. The progress notes should detail the facts and opinions leading to that decision.

SUICIDE ATTEMPTS

Suicide attempts should always be treated despite the wishes of the patient. These patients are often "crying for help." They are also often in a pathological mental state that may be transitory or treatable. This situation is different from the patient who refuses life-sustaining treatment. The difference is that with refusal of care, the patients are not killing themselves—rather, they're refusing help that would keep them alive (uh, okay).

CULTURAL DIFFERENCES

A patient from another country/culture can present some ethical dilemmas. If family members of your elderly patient state a wish that their grandmother not be told about a terminal illness such as cancer, you can explain to your patient that she is very sick and ask whether she wishes to make these decisions or prefers to have them made by another. If the wish is the result of a particular custom, the patient often will want others to make the decisions. This can then be considered an **authorized delegation** of decision-making authority. If the patient says she wants to know everything and make her own decisions, you must side with the patient.

CONFIDENTIALITY AND PUBLIC WELFARE

The personal and medical information that a physician obtains from a patient is (ethically and legally) confidential. **But!** In general, if the condition or disease of a patient can endanger other persons, the physician is **legally and ethically obligated** to report the situation to the appropriate parties. Many specifics are straightforward and are addressed with legal statutes. Common examples are sexually transmitted diseases and conditions that could affect the operator of a motor vehicle; e.g., seizures and severe cardiac arrhythmias. Others are more difficult. A patient with a serious, highly infectious disease (e.g., TB, meningococemia) should not be allowed to infect others. These patients can be held against their will if their behavior is considered a threat to others. Some infectious diseases may necessitate informing the patient's employer (e.g., health care worker, food worker).

Adolescents are allowed to consent for some services without parental involvement in some states. Know the laws of your own state in this regard. Adolescent consent for contraception is protected under federal law by language in the federal budget that restricts individual states from passing teen contraceptive laws, if that state receives federal subsidies for health care. So, adolescent consent for birth control is acceptable in all states. Consent for abortion services, however, is state-dependent.

BRAIN DEATH

Physicians may stop treatment if a person is "brain dead" (loss of entire brain function, including brain stem). An EEG is **not** required for diagnosis. Organs can then be donated **without** patient's prior consent if the next of kin (or surrogate) gives permission, knowing that the patient would want that.

PHYSICIAN-PHYSICIAN vs. PUBLIC WELFARE OBLIGATIONS

The physician should **not** allow **any** incompetent or unethical conduct by other physicians. If you **know** of

Quick Quiz

- You see a colleague drinking shots in a bar shortly before his 12-hour shift in the ED. Are you obligated to inform anyone?
- Know all of the scenarios in the ethics topic!

such conduct, the evidence should be presented to the appropriate authority. This may be the division chief or ethics committee of the hospital. Most state and many county medical societies now have confidential treatment of impaired physicians. Physicians who strongly suspect another physician is chemically impaired are obligated to urge the physician to seek treatment. If this impairment may affect medical competence, the obligation is to report the “credible evidence” to the local medical society. Note: A physician cannot act only on hearsay, but must have credible evidence before reporting it.

DRUG RESEARCH

It is unethical to use socioeconomic differences in choosing patients for a drug study, unless the socioeconomic status is considered a variable. For example, you cannot ethically test a drug only on those who can pay for it. Conversely, you cannot ethically offer a free drug for research only to those in a lower socioeconomic status.

FINANCIAL CONFLICTS

The ACP ethics document is very clear that certain financial relationships are unethical:

- The physician must disclose to patients if he intends to refer them to a facility or research study in which the physician has a financial stake.
- The physician should not refer patients to a care facility where she holds a financial interest but is not employed.
- A physician may not pay another physician for referrals.
- A physician may not receive payment or gifts (even “small ones”) from device manufacturers or pharmaceutical companies for recommending or using their products.
- Physicians should not sell products out of their offices, unless they are meeting an unmet need of the community (e.g., selling crutches or walkers in a small town). Physicians should not sell supplements or cosmetics out of their offices.
- Physicians should not advertise using unsubstantiated or false statements nor should they omit necessary information.
- Physicians can and should act as expert witnesses to benefit society, but they cannot accept payment in

exchange for biased testimony. Fees charged should be for “reasonable time and expenses.”

SCENARIOS

Some scenarios:

- 1) A patient enters the hospital unconscious and near death with a terminal disease. What should the physician do if:
 - The patient has a properly executed living will that states no intubation, CPR, etc.
 - The patient has no living will, but family members say they strongly prefer the patient be allowed to die with dignity and without heroics.
 - Same as “a” but family members (many of whom are lawyers) say they want all possible heroic measures to be done—and threaten dire consequences if their wishes are not followed!
- 2) A patient comes to the ED with an extensive acute MI, is mentally competent, and refuses to be admitted despite being fully informed of the possible consequences. What do you do?
- 3) A respirator-dependent patient requests in writing to be extubated. What do you do?
- 4) A female health care worker who is found to have hepatitis B antigen positivity requests that you not tell her supervisor at the hospital where she works.
- 5) A man is diagnosed with inoperable metastatic cancer. He states to his physician that he does not want his wife to know.
- 6) A newly married man just finds out that he has a serious autosomal dominant genetic disease, e.g., Huntington disease. He requests that the physician not tell his wife.
- 7) A man finds out he is HIV-positive and requests that you not tell his spouse.
- 8) A woman with suspected meningococcal meningitis refuses to be admitted and wants to go back to work.

Answers:

- 1) The physician should:
 - Follow instructions in the living will.
 - In this situation the physician needs more information; needs to know the wishes of the patient, not the family!
 - Follow instructions in the living will; the contract is between you and the patient. Besides, so far, all living wills have upheld in court.
- 2) You must show caring for the patient’s situation, yet attempt to dissuade the patient from leaving. If the patient still leaves, it is prudent to have the patient sign out “AMA”—against medical advice (the patient is not legally required to do this). You cannot stop patients from leaving unless you think they are mentally incompetent or a danger to others (e.g., they want to drive home).

- 3) You need more information (mentally competent, fully informed, etc.). This is a problem with probable far-reaching consequences—not just for you, but for the patient's other doctors, the hospital, and the patient's family. First step is to contact the hospital's ethics committee. You may also need assistance from the patient's other doctors, family, psychiatry, and social services.
- 4) This health care worker has a direct obligation not to cause harm to the patients with whom she interacts. If she refuses to inform the hospital infection control team, then you are obligated to do so.
- 5) Although the physician can strongly encourage the man of his wife's moral right to know the situation, communicating this to the spouse is ultimately the patient's obligation and not the physician's.
- 6) In this case, the physician should first strongly encourage the man to tell his wife. If that fails, the last resort is for the physician to tell the wife because of the risk of harm to future children.
- 7) In all HIV cases, the physician must make sure that anybody at risk (e.g., through sexual contact or IV drugs) is notified. Whenever patients say they are going to do the notification, the physician must ensure it is done. Usually, this obligation is taken care of by the state health department.
- 8) This patient may be held against her will for the good of public welfare.

PREOPERATIVE CARDIAC EVALUATION

Preoperative evaluation of a patient to determine the risks of having a cardiac event in the perioperative period is a topic you must know.

There have been several guidelines produced by different medical societies. As of this writing, the AHA/ACC "Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery" is the most recent document, with a focused update in 2009 regarding the use of perioperative beta-blockers to minimize intraoperative cardiac risk.

These guidelines recommend 5 steps to be followed:

Step 1: Does the patient need **emergency noncardiac surgery**? If so, then the patient should proceed to surgery; perioperative surveillance and postoperative risk stratification and risk-factor management should proceed as best as possible.

If the answer is no, this is not emergent. Proceed to Step 2.

Step 2: Does the patient have an **active** cardiac condition?

- Unstable coronary syndrome (unstable or severe angina or recent MI, defined as more than 7 days but ≤ 1 month)

- Decompensated heart failure
- Significant arrhythmias: 3rd degree AV block, Mobitz II AV block, symptomatic ventricular arrhythmias, supraventricular arrhythmias (includes atrial fib!) with uncontrolled ventricular rate (> 100 bpm at rest), symptomatic bradycardia, new ventricular tachycardia
- Severe valvular disease: any symptomatic aortic stenosis, asymptomatic aortic stenosis with gradient greater than 40 mmHg, symptomatic mitral stenosis

If so, then the patient should undergo evaluation and treatment before noncardiac surgery.

If these are not present, proceed to Step 3.

Step 3: Is the patient undergoing **low-risk surgery**? Here, the guideline gets murky. It is definite with defining very low-risk as superficial and ophthalmologic procedures, and the highest-risk as major vascular procedures. It lists endovascular abdominal aortic aneurysm repair and carotid endarterectomy as intermediate-risk. After listing these specifically, it goes on to state: "The physician must exercise judgment to correctly assess perioperative surgical risks and the need for further evaluation." Wow, thanks guideline ... In general, though, any procedure that is "ambulatory" in nature and does not require "hospital admission" is usually considered low-risk. Other surgeries in this category include all breast surgeries and endoscopic procedures.

So, if you get to Step 3 and the surgery is low-risk, proceed with surgery; if not, go to Step 4.

Step 4: Does the patient have **good functional capacity** without symptoms? If this is true, proceed with moderate-to-high-risk surgery.

What is a simple, easy method to assess functional capacity? The guideline recommends using a MET level of ≥ 4 . Now let's review that "MET" thing again. Remember that functional capacity can be expressed as metabolic equivalents (METs); 1 MET is the resting or basal oxygen consumption of a 70-kg, 40-year-old man in a resting state. Functional capacity is classified as excellent (> 10 METs), good (7–10 METs), moderate (4–7 METs), poor (< 4 METs), or unknown. Think of 4 METs as equivalent to carrying groceries up the stairs. Examples associated with < 4 METs include slow ballroom dancing, golfing with a cart, and walking at a speed of 2–3 mph. Activities that require > 4 METs include moderate cycling, climbing hills, skiing, singles tennis, and jogging. There are several scales (e.g., Duke Activity Status, Specific Activity Scale) out there, but, in general, this guide will help you.

So if the patient can run up a hill or mow his lawn without problems, then he likely can proceed with his planned surgery. If he can't, then we go to Step 5.

Quick Quiz

- What type of preoperative evaluation is done if a patient requires emergent noncardiac surgery?
- Know the 5-step process used in determining if a patient requires a pre-op cardiac evaluation.
- Which patients are started on beta-blockers before surgery?
- Know the pre-op screening labs and who gets them.

Step 5: Here, we have the patient who has gotten to Step 5 because of either poor or unknown functional capacity, and we must use clinical risk factors to help us determine if he can proceed to surgery.

The 5 clinical risk factors to ask about:

- 1) History of ischemic heart disease (history of MI + exercise stress test, current chest pain, nitrate use, ECG with pathologic Qs)
- 2) Heart failure history (prior or compensated)
- 3) Cerebrovascular disease history
- 4) Diabetes requiring insulin
- 5) Renal insufficiency (creatinine > 2 mg/dL)

If > 3 risk factors are present, the surgery-specific risk is important (Table 10-9). The guidelines say, for "... intermediate-risk surgery, there are insufficient data to determine the best strategy (proceeding with planned surgery with tight heart rate control with beta-blockade or further cardiovascular testing if it will change management)."

Bottom line: Aortic, major vascular surgery or peripheral vascular surgery generally requires further cardiac evaluation. Low-risk procedures (endoscopic, superficial, cataracts, breast surgery, or any ambulatory surgery) do not. Intermediate ... it's up to your judgment.

Scenarios you are likely to encounter:

- A low-risk patient who can proceed directly to surgery of any type without noninvasive testing

Table 10-9: Risk of Procedure; AHA/ACC

Low Risk	Endoscopies, local biopsies, breast biopsies, vasectomy, cataract surgery
Intermediate Risk	Surgeries: Carotid endarterectomy, intraperitoneal, intrathoracic, orthopedic, prostate, head and neck
Major Risk	Surgeries: Aortic and major vascular, cardiothoracic, emergent major surgery, long procedures with large blood loss and/or fluid shifts

- A moderate-risk patient with good functional capacity who can go directly to a non-vascular surgery
- A major-risk patient who needs further workup as defined in the charts prior to going to surgery

Beta-blockers: Know that high-dose beta-blockers used perioperatively, given without a history of dose titration, in beta-blocker-naïve patients do reduce primary cardiac events **but** carry an increased risk of mortality and stroke—hence, they are **not** recommended.

Who gets beta-blockers?

- **Vascular surgery** patients with **positive pre-op stress tests**.
- Continue these in patients **already receiving** them for angina, arrhythmias, or HTN.
- Beta-blockers should be titrated when used in order to avoid significant bradycardia or hypotension. Their use is not without risk.

PRE-OP SCREENING LABS

General guidelines follow, and are based on, an amalgam of various societies' recommendations!

Hematocrit:

- > 65 years of age for major surgery
- All surgeries that will/could result in major blood loss
- **Not** for minor surgery!
- CBC is **not** recommended unless cheaper than hematocrit alone

Electrolytes: **Not** recommended unless history suggests reason to check

Creatinine:

- > 50 years of age
- Major surgery
- Hypotension is likely
- Nephrotoxic drugs to be used

Glucose, liver function tests, PT/PTT, U/A: **Not** recommended unless clinical signs/symptoms warrant

ECG:

- Yes for all vascular procedures
- Nonvascular procedures:
 - Men > 45 years
 - Women > 55 years
 - Known cardiac disease
 - Clinical evaluation suggests possible cardiac disease
 - Diuretic use (electrolyte abnormality possible)
 - DM, hypertension, renal insufficiency
 - Major surgical procedure

CXR:

- > 50 years of age for major surgery
- Suspected cardiac or pulmonary disease

PFTs:

- **Not** recommended for healthy patients prior to any surgery
- Use for dyspnea that is unexplained

Stents and such: Hold off on elective **non**cardiac surgery if:

- Within 4–6 weeks of bare-metal stent placement
- Within 12 months of drug-eluting stent if patient must stop thienopyridine/aspirin
- Within 4 weeks of balloon angioplasty

PERIOPERATIVE MEDICINE MANAGEMENT

Anticoagulant:

- Minor surgery—continue.
- Major surgery:
 - Stop IV heparin 6 hours before surgery.
 - Stop LMWH 12–24 hours before surgery.
 - Stop warfarin 3–5 days before surgery. (Use a heparin bridge for those who need it.)

Antiplatelet:

- ASA—continue for minor surgery or in those with recent (6 months) MI, PCI, stroke; for major surgery stop 5–10 days before surgery.
- Clopidogrel—stop 3–7 days before surgery.
- NSAIDs and COX-2—stop 1–3 days before surgery.

Cardiovascular: Continue β -blockers, calcium channel blockers, nitrates, ACEIs, ARBS, and statins. Diuretics and cholestyramine are usually held.

Estrogen: Discontinue hormone replacement several weeks before surgery (or continue oral contraceptives and increase level of DVT prophylaxis).

Diabetes agents:

- Oral hypoglycemics—stop 12–72 hours before surgery depending upon half-life of drug and risk of hypoglycemia.
- Intermediate-acting insulin—give 1/2 to 2/3 of usual a.m. dose.
- Basal insulin—continue or reduce dose.

Psychiatric meds:

- MAOI—stop 10–14 days before surgery.
- SSRIs—consider withholding 2–3 weeks before neurosurgery.
- Antipsychotics—continue.

- Tricyclic antidepressants and lithium—continue, but some taper and discontinue several days before surgery.

Neurologic:

- Anticonvulsants—continue.
- Antiparkinsonian—continue, but some discontinue the night before surgery.
- Alzheimer drugs—discontinue.

PREVENTIVE MEDICINE

PATIENT EDUCATION

Know this entire topic. Consider all of Patient Education highlighted.

Because patient education improves outcomes, **periodically review** and **counsel** patients on the following:

- Tobacco
- Firearms
- Alcohol/substance abuse
- Physical activity level
- Obesity

Check the elderly for functional status, gait abnormalities, and for osteoporosis risk factors.

Teach males about self-examination of the **testes**.

Guide all patients about self-examination for skin disease, gum disease, STDs, and nutrition.

Recommend seat belts and good fluid intake.

Got all that?

Teaching women to perform a **breast self-exam** does **not** reduce their mortality from breast cancer, so most organizations are **no longer recommending** it.

Firearm-related injury and death is a **major** public health problem. The physician's ethical role is to counsel patients about firearm safety and to become involved in community efforts to prevent firearm injuries.

Smoking Cessation

Tobacco smoke is responsible for 90% of all lung cancer deaths and more than 10% of cardiovascular deaths.

The Agency for Health Care Policy and Research (AHCPR) Smoking Cessation Clinical Practice Guideline (2008 Update): At each patient visit, ask about tobacco products. The AHCPR guideline even recommends that tobacco usage be added as the fifth "vital sign." If the patient smokes, give strong, clear, personalized antismoking counseling. If the patient is willing to quit, set a "quit date" (preferably within 2 weeks), recommend pharmacologic therapy (see below), provide personal or group counseling, and schedule a follow-up visit. Tell discouraged smokers that **most** previous smokers required many (> 5) attempts to quit.

Quick Quiz

- What patient education topics should you review and counsel patients about periodically?
- Memorize [Table 10-10](#)!

Know that cessation of smoking can **exacerbate** ulcerative colitis.

First-line medications for anti-smoking:

- Bupropion SR
- Nicotine (gum, inhaler, lozenges, nasal spray, patch)
- Varenicline (Chantix®)

Counseling + meds: better than counseling alone.

Varenicline is a partial agonist of nicotinic acetylcholine receptors and is associated with **serious neuropsychiatric side effects** (behavior changes, suicidal ideation and behavior, and depressed mood).

Note that **cigar** smoking increases the risk of coronary heart disease (relative risk = 1.27), COPD (1.45), and cancers of the mouth and throat (2.02).

Other Disease Risks

Increases risk of disease:

- High intake of red meat increases risk of colorectal cancer.
- Alcohol increases risk of colon, breast, esophageal, and oropharyngeal cancers.
- **Obesity** is associated with increased risk of colon, breast, endometrial, kidney, and esophageal cancers—and may increase risk for prostate, ovary and cervix, liver and gall bladder, and pancreatic cancers, myeloma, and lymphoma! (Is there anything left?)
- Bladder cancer is inversely associated with fluid intake. Incidence in the high-fluid intake group is half that of those in the low-fluid intake group.
- Organisms that cause or increase the risk of cancer: HPV, HBV, HCV, HIV, EBV, and *H. pylori*.

Decreases risk of disease:

- High intake of tomatoes decreases prostate cancer risk.
- Fiber reduces heart disease and diabetes. Not sure about cancer, though.
- Vitamin D may decrease colorectal and prostate cancer risk.

Note that supplemental vitamins and minerals do **not** decrease cancer risk in patients with **adequate** diets.

Certain drugs are used to **decrease** cancer risks in special patient populations:

- Tamoxifen and raloxifene decrease breast cancer.
- NSAIDs and aspirin decrease colon polyps and colon cancer.
- Dutasteride (and probably finasteride) decreases prostate cancer.

SCREENING EXAMS

Overview

Screening protocols: [Table 10-10](#) provides a rough summary.

Every official entity detailing screening protocols has a different, but usually similar, suggested protocol for each disease. In the following, abbreviations used are:

ACP = American College of Physicians

ACS = American Cancer Society

NCI = National Cancer Institute

USPSTF = U.S. Preventive Services Task Force

Cardiovascular Disease

Blood Pressure and Cholesterol

Blood pressure: every 2 years and **every** clinical encounter.

Cholesterol: Screen men 35–65 years old and women 45–65 years old every 5 years. If the patient is placed on lipid-lowering agents, then generally they are checked every 6 months to a year thereafter. If the screening total cholesterol is near the threshold, it should be repeated periodically. See the Endocrinology section, Book 4, for treatment.

Table 10-10: Screening Exam Recommendations

Counseling about smoking	Each visit
Counseling, other	Initial visit and then periodically*
Blood Pressure	Each visit; at least every 2 years
Cholesterol	Every 5 years is appropriate
Breast Exams	Controversial*
Mammograms	Yearly after age 50*
Digital Rectal Exam	Yearly after age 50
FOBT	Yearly after age 50 (not needed after colonoscopy)
Colonoscopy	See GI section, page 1-33
Pap Smear	Every 3 years*
PSA	Inconclusive*
* See text for more information	

The Endocrinology section also discusses the recommendations for lipid screening contained in the latest document from the National Cholesterol Education Panel (NCEP), entitled Adult Treatment Panel III (with the relevant update from 2004). NCEP is an advisory group formed out of the National Heart Lung and Blood Institute (NHLBI), which is a subset of NIH (as is NCI). The ATP III (and update) screening recommendations vary slightly from the ones listed above but not by much.

The same situation is true for BP recommendations contained in the latest document from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7, 2003)—also an NHLBI advisory group. We discuss JNC7 in the Nephrology section, Book 2. Again, slight differences.

Both ATP III and JNC 7 are due for an update soon.

Estimating Cardiovascular Risk

For patients who do not currently have heart disease but have at least 2 risk factors for heart disease (per NCEP ATP III criteria—see the Endocrinology section, Book 4), know to estimate their 5-year, 10-year, or lifetime risk for heart disease using one of the many established risk predictor models (e.g., Framingham Risk Assessment). The result gives you good insight into how aggressive you need to be about reducing their cardiovascular risk factors.

Diabetes

The American Diabetes Association (ADA) recommends **annual** screening with a venous fasting plasma glucose (not a fingerstick!) for people > 45 years of age if they have no risk factors. Start earlier if they have risk factors such as obesity and/or a family history.

Retest in 3 years if normal.

The American Association of Clinical Endocrinologists recommends starting screening at age 30 if **any** risk factors are present.

Abdominal Aortic Aneurysm

One-time screening for abdominal aortic aneurysms (AAAs) is recommended in men age 65–75 if they have a history of smoking (ACC/AHA and USPSTF) or in men > 60 if they had a sibling or parent with AAA (ACC/AHA). Repeat screening is not recommended. No organization recommends screening in women.

Breast Cancer

Breast cancer screening using breast self-exams, clinical breast exams, and mammography is now somewhat controversial. We discuss the topic in the Oncology section, Book 4.

Prostate Cancer

Prostate Specific Antigen (PSA) testing has contributed to the increased finding and treatment of early prostate cancer. Although no trials have been concluded indicating its effectiveness as a screening test, consumer demand has made it a commonly performed lab test.

The American Urological Association and ACS recommend PSA and digital rectal exam yearly for men > 50 years old.

The ACP recommends that annual PSA be **discussed** with men between the ages of **50 and 69** to determine if they want it based on benefits and harms. **No** PSA screening is recommended for men > 70 years. In general, discuss screening at age 40 with African-Americans and in patients with a family history of early prostate cancer. The **digital rectal** exam, previously combined with serum PSA screening, is **no longer recommended** by the ACP.

To add to the confusion, the 2012 USPSTF guidelines recommends to **not** perform any PSA screening!

Prostate cancer screening may reduce prostate cancer specific mortality, but it does not appear to reduce all-cause mortality.

Colorectal Cancer

This is discussed in depth in the Gastroenterology section, Book 1.

Cervical Cancer

Pap smears have been proven effective, but the recommended intervals between these tests vary. Most recommend starting at age 21. When there have been 3 negative results with annual exams, continue every 3 years until 65 years old. If previous Pap smears have been negative and the patient does not have new sexual partners, patients > 65 years old do **not** need further smears. You do not need to get a Pap on women who have had hysterectomies for benign disease. See the Oncology section, Book 4, for workup of abnormal Pap smears.

HPV testing is recommended if the Pap smear cytology returns with atypical squamous cells of undetermined significance (ASCUS). Usually, the HPV test is collected with the Pap smear, but it is saved until cytology results are available. If ASCUS is discovered, then the lab is instructed to perform the HPV test (termed “reflex testing”). Women with ASCUS and the high-risk HPV types (e.g., 16, 18, 31) then go to colposcopy (instead of sending everyone with ASCUS to colpo; cuts down on unnecessary procedures). Other abnormalities on Pap smear almost always go to colposcopy.

Lung Cancer

Screening with imaging is **not** recommended currently. Tobacco cessation counseling is the most effective strategy.

Quick Quiz

- Should you do PSA screening in a 75-year-old man?
- When should Pap smears be initiated?
- What are the procedures and tests that you should consider for general management of an obtunded patient?

Vaccinations

Common adult vaccinations are discussed in the Infectious Disease section, Book 1.

MANAGED CARE ISSUES

ACCOUNTABLE CARE ORGANIZATION (ACO)

Overview

This was introduced in 2009 as a potential new model of care for which the Centers for Medicare and Medicaid Studies (CMS) is encouraging demonstration projects. This is a health care delivery and reimbursement model that ties the reimbursement to the quality of health care delivered and the total cost of care.

Example: 4 regional hospitals combine their outpatient services to better serve the local population. Primary care and specialists from each of the 4 hospitals participate. The costs of the services are bundled to meet predetermined budgets, which include incentives to meet specific performance improvement objectives.

ACO “Never Events”

These are events that occur (in the inpatient setting usually) that typically should not occur if the patient is receiving competent health care. These events, commonly called “never events,” are **not** reimbursed by CMS:

- Foreign object retained after surgery
- Air embolism
- Blood incompatibility
- Pressure ulcer stages III and IV
- Falls and trauma (including fracture, burn, electric shock)
- Catheter-associated UTI or vascular-catheter infection
- Manifestations of poor glycemic control (DKA, hyperosmolar, hypoglycemia)
- Surgical site infection including mediastinitis following CABG
- Infection, DVT/PE following hip or knee replacement
- Death/disability associated within a facility due to medication error, electric shock, burn, fall, use of restraints, or contaminated drugs

- Incident due to wrong oxygen or other gas
- Impersonating a health care worker (physician or nurse!)
- Abduction of patient
- Sexual assault within or on facility grounds
- Surgery on wrong body part, patient, or vice versa
- Implantation of wrong egg
- Infant discharged to wrong person
- Death/disability due to patient elopement
- Patient suicide or attempted suicide resulting in disability

POISONINGS

OVERVIEW

The following ingestions and inhalations are those **most likely** to cause death in the U.S.:

- Carbon monoxide inhalation
- Overdoses of analgesics, sedatives, or antidepressants
- Ingestions of isopropyl alcohol, methanol, or ethylene glycol
- Use of illicit drugs

First, we discuss an empiric approach to overdoses; then we focus on individual ingestions. Ingestions with HAGMA (high-anion gap metabolic acidosis) and increased osmolar gaps are covered exhaustively in the Nephrology section, Book 2. CO poisoning is discussed in the Pulmonary Medicine section, Book 2.

OVERDOSE MANAGEMENT

General management of the obtunded or comatose patient is guided by a history, vital signs, and physical exam. Assessment of **airway** is most important, with immediate intubation of the patient with unstable vital signs and/or inability to protect the airway. Next, assess rhythm with an ECG and continuous cardiac monitoring, and blood oxygenation with pulse oximetry.

The following interventions are usually empirically performed, except as noted:

- IV D50 if blood glucose low.
- Thiamine 100 mg IM or IV.
- ABG +/- carboxyhemoglobin level, serum basic chemistry, and general toxicology screen. Be sure to calculate the serum anion and osmolar gaps. Measure salicylate level if AG is increased.
- Serum acetaminophen level.
- Serum CPK, if patient was immobilized for long periods.
- CXR and supplemental oxygen prn.
- Naloxone IV if you suspect opiate overdose, but be careful of dose (see [Analgesics on page 10-35](#)).

Be able to characterize the patient's physical exam and determine whether the presentation is most consistent

Table 10-11: Physical Exam in Toxic Ingestions

Physical Exam	Category	Examples
“Excited”: Agitation, restlessness, hypertension, tachycardia, hyperventilation, hyperthermia, mydriasis (usually)	Anticholinergics	• Antihistamines • Neuroleptics (chlorpromazine, quetiapine) • Tricyclic antidepressants • Atropine • Antispasmodics (hyoscyamine) • Plants: Nightshade (belladonna) and jimson weed
	Sympathomimetics	• Ephedrine • Dextromethorphan (5–10x therapeutic dose) • Cocaine • Amphetamines • Methamphetamine • MDMA (“Ecstasy”) • 4-bromo-2,5-dimethoxyphenethylamine (“2CB”) • 2,5-dimethoxy-4-(N)-propylthiophenethylamine (“Blue Mystic”)
	Hallucinogens	• Lysergic acid diethylamide (LSD) • Mescaline (peyote) • Phencyclidine (PCP, “angel dust”) • Psilocybin (found in certain mushrooms)
“Depressed”: Obtundation, hypotension, bradycardia, hypoventilation, hypothermia, miosis (usually)	Cholinergics	• Organophosphate and carbamate insecticides
	Sympatholytics	• Clonidine
	Opiates	• Oxycodone (frequently combined with acetaminophen; has extended-release formulations; ETH-Oxydose™, OxyContin®, OxyIR®, Roxicodone®, Percocet®) • Hydrocodone (frequently combined with acetaminophen; has extended-release formulations; Lorcet®, Lortab®, Vicodin®, Zydone®, Co-Gesic®, Hycet®, Magesic®)

with “**excitation**” or “**depression**” and know which ingestions are associated with the presented scenarios (Table 10-11).

In clinical practice, many patients present with co-ingestions, and the physical exam can be a mixed bag of signs/symptoms.

Tip: Mydriasis = dilated pupils (big word, big pupils); miosis = constricted pupils (small word, small pupils).

After the patient is stabilized, consider gastric lavage with a large bore orogastric tube; this may be effective even hours after ingestion if the drug was ASA, anticholinergics, or narcotics. (These drugs cause decreased gastric motility.) Lavage with only small amounts of tap water (100 cc) to prevent forcing the stomach contents into the duodenum. Follow with activated charcoal and a cathartic (sorbitol or Mg citrate). Know that activated charcoal is **not** effective when the overdose is with the **metals** lithium and iron. Continued dosing with oral charcoal is effective in decreasing the levels of a few drugs by **gut dialysis** (absorption via the enteric recirculation)—especially digoxin, phenobarbital, theophylline, tricyclics, and salicylates.

Note: There is a strong trend toward **not** lavaging patients with most overdoses. The thought is that lavage

is, in most cases, ineffective; using activated charcoal with cathartics is at least as effective, if not more so.

Shock is treated with CVP monitoring, IV fluids, +/- dopamine.

Alkalinization and acidification of the serum (and hence, the urine) are based on the principle that compounds in their ionized form are **less tissue-permeable** and **more easily eliminated** by the kidneys. Weakly acidic substances ionize in an alkaline environment while weakly alkaline substances ionize in an acidic environment. Alkalinization of the urine to a pH of > 7 increases excretion of ASA, tricyclics, and phenobarbital. Acidification of the urine with ammonium chloride increases excretion of amphetamine and phencyclidine (PCP). Mix 2.75 mEq/kg in 60 cc NS and give through the gastric tube. Clamp for 1 hour. Repeat q 6 hours until urine pH < 5.0.

Important: Hemodialysis may be necessary in patients with severe overdose or renal failure. It is effective in removing drugs with **low molecular weights** that are **not** lipid soluble, protein bound, or tissue bound—i.e., drugs with a small volume of distribution. These include lithium, chloral hydrate, salicylates, and alcohols (methanol and ethylene glycol). Dialysis is not effective in removing benzodiazepines, opiates, or tricyclics.

Also: Charcoal hemoperfusion (blood pumped through a charcoal filter), in contrast to dialysis, removes drugs

Quick Quiz

- Activated charcoal is not used for what overdoses?
- For tricyclic overdose, what should you do to the urine? For what other overdoses does this work?
- Methanol causes what neurologic deficit?
- Does ethylene glycol cause an increased osmolar gap, anion gap, or both?

that **are** lipid soluble and protein bound! It can also remove some of the same drugs as dialysis. Also, like dialysis, it is most effective in removing drugs with a **low** volume of distribution (V). Charcoal hemoperfusion is especially good for digoxin, theophylline, and salicylate overdoses.

SPECIFIC TOXINS

Refer to [Table 10-11](#). Also see [Table 10-12](#) for a summary of common poisoning agents and their usual antidotes.

Anticholinergics

Don't forget the presentation of anticholinergic intoxication (discussed above and reiterated in [Table 10-11](#)). "Red as a beet; dry as a bone; hot as a hare; blind as a bat; mad as a hatter; full as a flask."

- Red: Cutaneous vasodilation
- Dry: Anhidrosis
- Hot: Hyperthermia
- Blind: Mydriasis
- Mad: Hallucinations
- Full: Urinary retention
- Antidote: Physostigmine

Acid Alcohols

Isopropyl alcohol ("rubbing alcohol") is a common solvent and disinfectant. Like ethanol, it has **CNS-depressant** effects. It is second to ethanol in the causes of alcohol overdose. The main metabolite is acetone, which causes a prolonged CNS effect. The acetone causes ketonuria but no anion gap acidosis, and the **sweet odor** of acetone is evident on the patient's breath. CNS depression is the major effect, although there may also be cardiac depression. Abdominal pain and vomiting are usually present. An **osmolar gap** of > 35 mOsm is usually seen with toxicity. Treatment: Give supportive care, including lavage if < 2 hours has passed since ingestion. Make early use of **hemo/peritoneal dialysis** in severe cases.

Methanol (wood alcohol) toxicity is usually due to contaminated moonshine. It is only mildly inebriating, and

many signs of toxicity are delayed > 24 hours—especially visual impairment, from blurring to **blindness**. The toxic metabolites are formaldehyde and formic acid. Serum analysis shows an increased anion **and** osmolar gap. Treat with fomepizole, folic acid, and immediate dialysis. Give folic acid to increase metabolism of the formic acid.

Ethylene glycol (antifreeze). Alcohol dehydrogenase breaks down ethylene glycol to its very toxic metabolites, especially oxalate. Presence of oxalate is indicated by **calcium oxalate crystals** in the urine and **hypocalcemia** (oxalate chelates calcium). Suspect if a patient appears intoxicated but without an alcohol smell, and with a HAGMA and **increased** osmolar gap. Treat with **fomepizole**, bicarbonate for the acidosis, calcium prn, and **immediate dialysis**.

Analgesics

Opiates

Think opiate overdose (especially on a Board exam) when you see the following **combination** of signs/symptoms: obtundation, hypoventilation (decreased rate and tidal volume), decreased bowel sounds, and **constricted pupils**. Know that meperidine, propoxyphene, and tramadol are associated with **seizures** in intoxicated patients (especially those on dialysis!); and methadone can increase the QT interval, causing *torsades*.

Naloxone is usually given IV in doses of 2 mg, up to a maximum of 10 mg. The drug should be used to **reverse hypoventilation** induced by opiates—it should **not** be used in large doses as a **diagnostic** tool for opiate intoxication because of the risk of inducing withdrawal in the chronic user. The dose of naloxone should be titrated to result in **normal ventilation** (10–14 breaths/minute), not consciousness. Too great of a dose (enough to wake someone up completely) can cause rapid reversal and withdrawal. Too small of a dose can result in a need for

Table 10-12: Toxins and Antidotes

Toxin	Antidote(s)
Acetaminophen	N-acetylcysteine
Digoxin	Ag-binding fragment
Opiates	Naloxone
Benzodiazepines	Flumazenil (Mazicon®)
Nitrates	Methylene blue
Iron	Deferoxamine
Carbon monoxide	Oxygen
Ethylene glycol	Fomepizole
Methanol	Fomepizole
Organophosphates	Atropine, Pralidoxime
Cyanide	Nitrates, Na-thiosulfate

intubation. Chronic users of opiates, and those patients who inhaled or ingested a large dose of the drug, may require an intravenous drip of naloxone because its half-life is very short. Usually 2/3 of the dose that results in adequate ventilation is given per hour in a drip.

Know that **acute lung injury** is sometimes seen in opiate addicts who undergo **rapid reversal** of unconsciousness with naloxone + high-flow oxygen via facemask. Patients usually recover with supportive care.

Also recognize that naloxone is usually **not** the correct answer if a scenario presents a patient with dilated pupils.

Salicylates

Salicylates are metabolized in the liver by conjugation with glycine or glucuronide. These pathways are quickly saturated in a person who has overdosed, resulting in **acidemia**. The increased ASA level initially causes hyperventilation through a **central** effect. This has a protective effect since the ASA crosses the blood-brain barrier (i.e., is more tissue permeable) when the system is acidemic. Acidosis can worsen if the HAGMA is compounded by lactic acidosis due to pulmonary edema. If the patient stops hyperventilating, it is probably due to respiratory muscle fatigue.

The classic presentation of the patient with an ASA overdose is tachypnea and a mixed acid-base disorder (**HAGMA + respiratory alkalosis**) and a history of having taken “over-the-counter” pain medicine. Depending on the dose, patients may additionally complain of tinnitus.

Treatment of salicylate overdose: Decontamination with activated charcoal with cathartic, and **serum/urine alkalinization** using sodium bicarbonate. Both hemodialysis and charcoal hemoperfusion have been used in severe cases (salicylate levels > 100 mg/dL). The charcoal hemoperfusion removes the salicylates better than hemodialysis but does not correct any fluid/electrolyte imbalance. (Patients are often hypokalemic.)

Acetaminophen

90% of this drug is metabolized in the **liver**, by glucuronidation or sulfation, to inactive metabolites. 5% is excreted unchanged through the kidneys. The last 5% is metabolized by way of the hepatic cytochrome P-450 system to active metabolites. One of the active metabolites is N-acetyl-p-benzoquinoneimine (**NAPQI**), which is highly **hepatotoxic**. Normally, the small amount of NAPQI is quickly detoxified by reacting with the sulfhydryl group of glutathione, forming nontoxic mercapturic acid. A large overdose results in depletion of the glutathione and subsequent increase in these metabolites. A severe overdose is often followed by mild N/V/D. It is only after 24–48 hours that liver toxicity ensues.

Many **intentional** overdose patients present with **co-ingestion** of multiple substances. Always suspect acetaminophen as part of the clinical picture of any overdose.

It is standard to check acetaminophen levels **regardless** of the presentation—because untreated toxicity is potentially fatal.

Alcohol-acetaminophen syndrome. Chronic moderate-to-heavy use of **alcohol** has a **2-fold** effect: The cytochrome P-450 system is cranked up (so that more NAPQI is produced), and the amount of glutathione is decreased (so less is available for detoxifying the NAPQI). Therefore, long-time users of moderate-to-heavy amounts of alcohol who take acetaminophen in normal or higher doses are at risk for severe hepatic toxicity or liver failure.

Treatment of acetaminophen overdose: **Activated charcoal** is beneficial, does not hinder use of N-acetylcysteine (**NAC**), and is usually used if patients present within 4 hours of ingestion. Although there is great variability in the hepatic response to the overdose, a 4-hour post-ingestion acetaminophen level of > 250 µg/mL indicates a high probability of hepatotoxicity—if untreated. NAC is an effective antidote that works by increasing the availability of hepatic glutathione.

NAC is effective when given within **8 to 16** hours after the acetaminophen overdose. Even when given late in the course to a patient with significant ingestion and toxicity, it reduces mortality and improves liver function. Treatment can be initiated with either an **IV** or **oral** protocol, which varies in their duration. IV is favored if patients are vomiting or present in liver failure.

The **oral** NAC protocol includes a loading dose of 140 mg/kg, followed by doses q 4 hours of 70 mg/kg for 17 doses. (**IV** uses loading of 150 mg/kg with an infusion over next 20 hours.) Both protocols continue dosing until the measured acetaminophen level is undetectable or “clearly decreasing” with a minimum of dosing over 20 hours. (The specific definition of “clearly decreasing” is controversial.)

Prescription Drugs

Theophylline: This drug more often presents as **inadvertent** toxicity rather than intentional overdose. Toxicity often occurs in the context of the patient having been prescribed another drug (or herbal preparation) that increases theophylline levels. Suspect toxicity when you see a clinical history of obstructive lung disease and tremulousness, tachycardia/ventricular arrhythmias, vomiting, +/- seizures with a theophylline level > 20 mcg/mL. This toxicity can look like cocaine or methamphetamine use. Be aware of it in patients with asthma who also use these illicit drugs! Know the drugs that commonly interact with theophylline and increase levels: CYP3A4 inhibitors, certain macrolides, quinolones, and zileuton.

Treat with supportive care (paying attention to **hypokalemia** because it predisposes to ventricular arrhythmia) and multiple doses of activated charcoal with cathartic. If vomiting is too severe to allow for charcoal, give

Quick Quiz

- What is the common acid-base disorder typically found when a patient presents with ASA overdose?
- What drugs are used to treat acetaminophen overdose?
- What ECG finding correlates most closely with the degree of intoxication of a tricyclic antidepressant?

ondansetron +/- ranitidine. Treat seizures with diazepam; SVT with adenosine. Stable ventricular arrhythmias usually respond to amiodarone; treat hypotension with alpha agonists (phenylephrine or norepinephrine). Oddly, beta-blockers can reverse hypotension, if the alpha agonists don't work, but beta-blockers should be given only under the guidance of a medical toxicologist. Call poison control to get such advice. Dialysis is recommended in patients with seizures or ventricular arrhythmias.

Lithium: Mental status changes are the most common manifestation of overdose—affecting > 90%. Other CNS changes include seizures and symptoms due to encephalopathy (poor memory, incoherence, disorientation). Patients may also get parkinsonian symptoms and movement disorders. Nausea, vomiting, and diarrhea are also common. A lithium level is obtained for purposes of documenting definitive overdose, but symptoms do not correlate with levels.

Don't forget about the complications from chronic lithium use: renal tubular acidosis, nephrogenic diabetes insipidus, and sicca symptoms.

Treatment: Activated charcoal is **not** effective. Gastric lavage is recommended in this setting. Restore fluid and electrolyte balance, and use hemodialysis in severe lithium overdose cases. Consider severe intoxication when there are **any** symptoms characteristic of lithium poisoning, when the lithium levels are > 3.5 to 4 mEq/L, or when the serum level does not decrease appropriately.

Tricyclic antidepressants: These drugs are lipophilic and are protein-bound, so they have a very large volume of distribution and **cannot** be removed by dialysis. Clinical presentation of toxicity includes: sedation or confusion and arrhythmias.

Treatment includes gastric decontamination with activated charcoal with cathartic, if presentation is within 2 hours of ingestion. Give supportive care and monitor for cardiotoxic side effects. Tricyclics cause tachycardia and PR, QT, and QRS prolongation. The **QRS prolongation** is the ECG change that correlates most closely with the **degree** of intoxication! Ventricular tachycardia and fibrillation are also common. The cardiac problems often respond to maintaining an **alkalemic** state—either

by hyperventilation if the patient is intubated or with IV bicarbonate. Keep serum pH 7.5 to 7.55 using sodium bicarbonate ("alkalinizing the urine"). Give lidocaine (first choice) or phenytoin as needed for arrhythmias. Use benzodiazepines for seizures.

Digoxin: This drug is not commonly prescribed, but toxicity is **not** uncommon because the drug has a very narrow therapeutic index. Levels do **not** correlate with toxicity, so you have to pay close attention to signs and symptoms. Clinical presentation of toxicity includes anorexia, N/V, belly pain, confusion, weakness, changes in color vision, scotoma, and bradycardia with hypotension. The presentation can appear as if the patient is being overtreated with an antihypertensive drug—this is important because patients who take digoxin will often also take antihypertensives. Labs may show potassium disturbances (**hypo-** in **acute** toxicity; **hyper-** in **chronic** toxicity) and acute kidney injury, which is often the cause of the increase in the serum level.

Know the commonly used drugs that can increase digoxin levels when coadministered: diltiazem, verapamil, amiodarone. Because digoxin is cleared by the kidney, decreases in GFR increase the serum level.

Treatment consists of **continuous** cardiac monitoring. PVCs are common. Other conduction abnormalities include AV block with junctional escapes and serious ventricular arrhythmias. The ECG should be evaluated periodically because digoxin can flatten or invert T waves, shorten the QT interval, and depress lateral ST segments (findings often referred to as "dig effect").

Treat with activated charcoal if presented within 2 hours of ingestion. Treat patients who have serious ventricular arrhythmias (tachycardia, fibrillation, complete heart block, Mobitz II, and symptomatic bradycardia), serum K > 5 mEq/L, and renal failure or mental status changes with Fab fragments (a digoxin antibody). Be aware that presenting hyperkalemia will rapidly reverse with Fab antibodies, so do **not** be overly aggressive in treating **hyperkalemia**.

Much controversy exists about whether to give calcium to patients with hyperkalemia from digoxin toxicity (to stabilize cardiac membranes). Conventional teaching is to withhold the calcium (and this is what we have written in our Nephrology section, Book 2), but several case reports and retrospective studies show that calcium does not harm these patients. The current standard, however, is not to give calcium if you are giving Fab antibodies because the hyperkalemia is rapidly corrected, and arrhythmias are unusual.

Illicit Drugs

Cocaine: Cardiotoxicity can occur no matter what the route of use. This drug causes rhythm disturbances (including V fib/tach), ischemia (irrespective of whether the patient has preexisting atherosclerotic disease), myocarditis, and systolic dysfunction. Suspect use in a

young patient presenting with **MI**. Seizures and stroke are also common with cocaine; consider it in patients with first-time seizure. Know that beta-blockers are **not** used in this group to treat angina or verified myocardial ischemia. Instead, nitro, calcium channel blockers, and BDZs are 1st line treatments.

Methamphetamine is a powerful CNS stimulant that acutely increases the release of epinephrine, norepinephrine, serotonin, and dopamine. Consider overdose in the **sweaty**, severely agitated or psychotic patient with tachycardia and hypertension. Severe tooth decay occurs in chronic users. Acute treatment of the severely agitated patient is with IV **benzodiazepines** first and then antipsychotics, such as haloperidol, if needed. IM doses are given if unable to give IV. Watch for **rhabdomyolysis** in these patients by monitoring electrolytes, BUN, Cr, CPK, serum lactate, liver enzymes, and clotting times.

Phencyclidine (PCP) can cause acute psychotic agitation, seizures, dystonia (including laryngospasm), and hypertensive crisis. Severe dystonia can cause rhabdomyolysis. Treat with a calm environment and IV BDZs as needed, with supportive care for complications such as rhabdomyolysis.

Heroin is an opiate. Be careful with the use of naloxone in chronic users because of the risk of precipitating withdrawal if you overshoot in dosage. Heroin intoxication is sometimes difficult to differentiate from alcohol intoxication because both substances are CNS depressants. But alcohol usually does not constrict the pupils or decrease the bowel sounds.

MDMA (3,4-methylenedioxymethamphetamine; **ecstasy**) is commonly used by young people in the setting of parties or raves. Use results in feelings of euphoria, loss of inhibitions, cozy feelings of intimacy, and increased sexual arousal due to an increased release of serotonin. The drug is commonly perceived as being very mild with minimal risk and physical effects; but in actuality, ecstasy possesses properties that resemble a combination of amphetamines and peyote (stimulant + hallucinogen). The drug is taken in tablet form, and overdoses can result in death.

Side effects of MDMA include bruxism (jaw grinding), anxiety, sweating, hypertension, and tachycardia. **Dangerous complications** include severe hyponatremia, malignant hypertension, stroke, cardiac ischemia, arrhythmias, aortic dissection, and serotonin syndrome. Hyperthermia and rhabdomyolysis are possibilities, especially in patients who dance all night and use ecstasy.

Activated charcoal is given if the patient presents within 1 hour of ingestion. In intoxicated states, most symptoms respond to **benzodiazepines** (hypertension, tachycardiac, agitation). Haloperidol can potentially exacerbate hyperthermia. Arrhythmias respond to calcium channel blockers. Beta-blockers are **not** recommended because

of the possibility of unopposed alpha-adrenergic stimulation. Hyponatremia usually responds to water restriction; hyponatremic seizures should be treated with hypertonic saline.

LSD: Lysergic acid diethylamide is referred to as “acid” and causes hallucinations. Fatalities and morbidity during use are unusual—usually attributable to bad decisions being made while intoxicated.

Miscellaneous

Carbon monoxide: Carbon monoxide quickly binds with hemoglobin—with an affinity of ~ 250x greater than O₂. This carboxyhemoglobin (COHb) decreases arterial oxygen content, which leads to **tissue hypoxia**.

Symptoms are progressive and range from **headache** and **lightheadedness** to lethargy to unconsciousness to coma to **death**.

Be especially suspicious if the patient has been working around cars, gas/oil heating units, or generators. Typical real-life scenarios:

- Car exhaust: garage music band using a running car to warm up the garage on a cold **winter** day—with the door closed.
- Exhaust from gasoline-powered generators: Especially suspect after electricity has been lost, such as after a flood, hurricane, or ice storm.
- Poor combustion in heating unit: Suspect when a patient calls from home in **winter** (especially near start of the cold season) and says the family is suffering from headache and lightheadedness. The patient may sound slow to respond. Or the patient calls in the winter and complains of headache and lightheadedness, which improves when he goes outside.

What to do? The answer to any scenario in which the patient calls you with suspect symptoms, especially with the above environmental factors, is to tell the patient to leave and get the family out of the house immediately; then, you send an EMS unit there.

CO poisoning is responsible for most deaths in patients with **smoke inhalation**, so don't forget to check COHb levels when managing smoke inhalation.

The brain and heart are **especially** sensitive to CO. Poisoning often causes **long-term to permanent** CNS impairment with cognitive deficiencies (i.e., memory and learning) and personality and movement disorders.

Fetal hemoglobin has especially high affinity for CO, so treat pregnant patients aggressively.

If you suspect carbon monoxide poisoning, get a **carboxyhemoglobin level**. A hand-held breath analyzer can quickly rule **out** CO poisoning, but ethanol causes false positives:

- Mild-to-moderate CO toxicity occurs at 15–30%.
- Moderate-to-severe toxicity occurs if > 30%.

Quick Quiz

- A 30-year-old man presents with acute MI. What drug should be ruled out as the cause?
 - Know carbon monoxide poisoning!
 - What are the 3 drugs used to treat cyanide poisoning?
 - How do you check for ongoing inorganic lead exposure? What about exposure 2 years ago? What if 10 years ago?
 - What is the treatment for organophosphate poisoning?
- > 50% is often fatal.
“Cherry red” coloration is **rare**.

Treat CO poisoning with **100% O₂**—this decreases the half-life of COHb from about 5 hours to 1 hour. Hyperbaric O₂ further decreases the half-life to 30 minutes, but its main benefit is that it decreases the CO-induced ischemic reperfusion injury to the brain.

Hyperbaric oxygen is generally given for **moderate-to-severe** CO poisoning. Many centers routinely use it in all patients with a COHb level of $\geq 25\%$ and in pregnant women with a level of $\geq 20\%$. Use it for **all** patients presenting with either of the following:

- Loss of consciousness or any focal neuro deficit
- End-organ damage, especially acidosis

Smoke inhalation: Respiratory impairment results from the noxious chemicals in the lungs or laryngeal/airway edema. Suspect laryngeal involvement if face or airways are burned (e.g., singed nasal hairs). Don't forget about the association between CO poisoning and smoke inhalation.

Cyanide poisoning clues: Patient's breath has an **almond odor** and lab draw shows **bright red venous blood**. Cyanide immediately binds to the **ferric** molecule in the mitochondrial cytochrome oxidase complexes, thereby blocking cellular aerobic metabolism. These patients very quickly develop headache, tachycardia, and tachypnea. This may quickly progress to coma and various cardiac arrhythmias. Think about cyanide poisoning in patients who have been in a fire or who have received sodium nitroprusside or amygdalin (chemical derived from apricot and peach pits that is used often in herbal compounds). Laboratory evaluation routinely shows **significant** lactic acidosis. Diagnosis is **clinical**, after excluding other causes of lactic acidosis and carbon monoxide poisoning. Assays exist to find the chemical in the blood, but these are reference tests that take a long time to return.

Treatment for cyanide poisoning is the 3-step cyanide antidote package. Goal is to induce methemoglobinemia because cyanide preferentially binds methemoglobin and produces a less toxic reaction.

- **Step 1** is **amyl nitrite** held under the patient's nose for 30 seconds.
- **Step 2** is to administer 3% **sodium nitrite IV**. The nitrites convert hemoglobin to methemoglobin (the ferric form of hemoglobin), which more effectively competes with the cytochrome oxidases for the cyanide. Amyl nitrite inhalation causes a 3–5% methemoglobinemia while the sodium nitrite causes 20% methemoglobinemia.
- **Step 3** is **sodium thiosulfate IV**, which acts as a substrate for the enzyme rhodanese. This enzyme converts the cyanide released from hemoglobin to inactive thiocyanate, which is excreted renally.

Significant toxicity can result in a **parkinsonian-type syndrome** because cyanide is toxic to the basal ganglia.

Inorganic lead: There are 3 scenarios to test for lead exposure, depending on when the exposure occurred:

- 1) For **ongoing** exposure, check **whole blood** lead level.
- 2) **After** exposure has occurred, RBC protoporphyrin and zinc protoporphyrin levels will remain elevated for several months.
- 3) For evaluating the effect of exposure from **years before**, the best test is to measure urine lead 24 hours after giving 1 gm of EDTA.

Organic lead is lipid-soluble and rapidly excreted, and previous exposure is **not** detectable!

Insecticide: Organophosphate and carbamate poisonings present identically. Symptoms include increased salivation, miosis (small pupils), N/V/D, and abdominal cramps. Affected patients also complain of chest tightness and generalized weakness. Organophosphates are **more toxic** than carbamates; they bind **irreversibly** to acetylcholinesterase, whereas the carbamate binding is reversible. This is reflected by a decrease in the level of RBC (**not** plasma!) acetylcholinesterase for several months after organophosphate poisoning, while it returns to normal within hours after carbamate poisoning.

Treatment for insecticide poisoning: The route of the poison into the body is **dermal** absorption (especially organophosphates), so decontaminate by removing clothes and showering with soap. For moderate-to-severe symptoms, give **atropine** (1–2 mg IV, repeat q 5 min prn). Additionally, for organophosphates only (**not** carbamate), give 2-protopam (2-PAM) IV.

DRUG WITHDRAWAL

So far, the discussion has focused on intoxication. You should also know the following presentations of specific drug withdrawal.

Heroin is the major opiate associated with physiologic withdrawal—it also has the most addictive potential. Symptoms usually start within 6 hours to a day after the last dose of drug—or can present immediately in the setting of opiate antagonists (e.g., naloxone, buprenorphine). Early symptoms include agitation, rhinorrhea, tearing, muscle aches, nausea, vomiting, abdominal pain, and diarrhea. Definitely think about this entity in the tearful patient who is yawning—those two activities usually don't go together.

Exam shows **dilated** pupils, yawning, hyperactive bowel sounds. Tachycardia and hypertension are seen in patients in severe distress (but often are not present in most patients).

Methadone is given to patients who are chronically addicted to opiates and present in **acute** withdrawal. If the patient desires to stop opiate use entirely because of addiction and refuses methadone, symptoms can be ameliorated with clonidine and diazepam. Promethazine is given for vomiting, and loperamide helps the diarrhea.

Benzodiazepine (BDZ) withdrawal can be fatal. It presents with anxiety and tremulousness, melancholy, and sometimes psychosis/seizures. Time of withdrawal from last dose depends on whether the drug used has a short or long half-life (up to 3 weeks for diazepam). Ideally, these drugs would be tapered over a prolonged period when a patient is discontinuing chronic use. Withdrawal is treated with long-acting benzodiazepines.

Ethanol: Patients severely addicted to ethanol start having withdrawals within about 6 hours from the last drink (and can happen even though the patient still has a measurable blood alcohol level. If it's lower than the patient is accustomed to having, then he can withdraw). Symptoms get more severe as time passes. After about 12 hours, patients usually have an isolated generalized seizure. The next phase is hallucinosis, where the patient's sensorium is intact and BP/pulse are normal; but, he sees, hears, and feels nonexistent phenomena. The last withdrawal syndrome is delirium tremens (DTs). DTs are marked by autonomic instability and delirium. Untreated, they last about 5 days. Complications include volume depletion, hypokalemia, hypomagnesemia, and hypophosphatemia. For DTs, give good supportive care, replace thiamine with glucose, and give long-acting BDZs. Replace electrolytes prn. Watch out for refeeding hypophosphatemia (discussed in the Nephrology section, Book 2). For patients who can be frequently observed, give repeat BDZ doses when symptoms recur. In situations where observation is not as feasible, fixed dosing schedules are used. Do **not** use haloperidol for the delirium because it can precipitate seizures. Chlordiazepoxide can be given orally to patients not in DTs, if they desire to quit drinking, to prevent alcohol withdrawal.

OPHTHALMOLOGY

OVERVIEW

Aqueous humor is produced by the ciliary body, flows through the pupil into the anterior chamber, and then goes through the trabecular network and into the Schlemm canal. The greater the resistance to this flow in the trabecular network and the Schlemm canal, the greater is the intraocular pressure. Normal pressure is < 21 mmHg (Figure 10-6).

GLAUCOMA

Overview

Glaucoma is an insidious disease in which a prolonged, elevated intraocular pressure causes progressive visual field loss due to optic nerve damage. There are 4 broad classifications: primary open-angle (POAG), closed-angle, congenital, and secondary. Know the specifics about POAG and angle-closure glaucoma.

Primary Open-Angle Glaucoma

Primary open-angle glaucoma (POAG) is the most common type. It is called "open-angle" because the orb has elevated pressure with no closure of the inlet of the trabecular network. These patients suffer **unnoticed** gradual loss of peripheral vision (tunnel vision) that can progress to legal blindness before it is detected. Risk factors include advanced age, family history, African-American race (5x increased risk compared to other races), and increased intraocular pressure.

Be suspicious and refer for ophthalmologic evaluation those patients with risk factors and/or those who have "**cupping**" on fundoscopic exam. ("Cupping" = cup occupying > 50% of the optic disc; normal cup occupies < 50%.)

Screening of POAG: The American Academy of Ophthalmology (AAO) recommends a comprehensive eye exam by an ophthalmologist or skilled optometrist after the age of 40. After the initial screening exam,

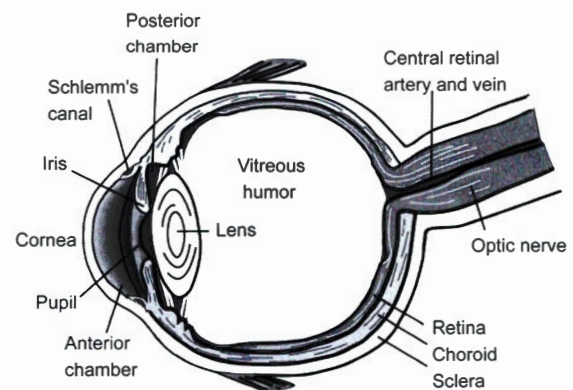


Figure 10-6: Structures of the Eye

Quick Quiz

- What is the difference between open-angle and angle-closure glaucoma? Which is a medical emergency?
- What is the treatment for open-angle glaucoma? What is the treatment for angle-closure glaucoma?
- Describe the findings with retinal detachment.
- What is the treatment for retinal detachment?
- How do retinal artery occlusion and retinal vein thrombosis differ?

repeat screening is usually recommended every 3–5 years in patients without risk factors and every 1–2 years for those with one or more risk factors (borderline intraocular pressure, cupping, African-American race, and family history). Patients with DM should be seen yearly. The AAO also recommends that African-Americans have periodic exams between the ages of 20 and 39 as well. For all individuals older than 60, a complete exam should be done every 1–2 years. The USPSTF found insufficient evidence to recommend for or against screening adults for glaucoma.

Treatment of POAG is with medications or laser surgery. The following meds are used:

- **Prostaglandins** (topical) are 1st line drugs because of the once-daily dosing and the few systemic side effects, especially compared to the topical beta-blockers. These are expensive!
- **Beta-blockers** (topical) dramatically decrease intraocular pressure—probably by decreasing production of aqueous humor. It is thought aqueous humor production is mediated by tonic sympathetic (beta) stimulation.
 - Nonselective (timolol, carteolol, levobunolol, metipranolol)—may cause lethargy, bradycardia, and exacerbations of COPD
 - Beta₁-selective (betaxolol)

Angle-Closure Glaucoma

Primary angle-closure (closed angle, narrow angle) glaucoma, the most severe form of narrow-angle glaucoma, is an **ocular emergency**—know it well. Risk factors include age > 40 years, female, **hyperopia** (farsightedness), Asian race, and family history. The elevated intraocular pressure is caused by mechanical obstruction of aqueous outflow through the trabecular network, due to an anomalous iris configuration or iris neovascularization. The resulting rapid increase in intraocular pressure causes redness, severe eye pain, nausea, and halos around lights. It can also be associated with headache and present similar to migraine. Low-light conditions that

precipitate pupillary dilatation (e.g., night time or in the movie theater) are associated with onset.

Physical exam shows decreased vision, increased intraocular pressure (often > 30 mmHg), a narrow anterior chamber (difficult to assess), corneal edema, conjunctival hyperemia, and a fixed, mid-dilated pupil.

Ideal treatment includes immediate ophthalmologic referral for a laser iridotomy. If an ophthalmologist cannot see the patient immediately and patient has decline in vision, institute immediate treatment:

- Place patient supine
- Give timolol 1 drop, wait 1 minute, then
- Give apraclonidine 1 drop
- Give pilocarpine 1 drop
- Give prednisone 1 drop
- Give acetazolamide

Instructions with over-the-counter medications often include admonitions to “avoid use in patients with glaucoma” (**decongestants**). These warnings apply **only** to patients with angle-closure glaucoma not already treated with iridotomy.

THE RETINA

Retinal Detachment

Retinal detachment may occur spontaneously. It often presents as flashes or streaks of light (photopsias), showers of black dots (hemorrhage), or a “shade coming down” or “waving curtain” in a portion of the visual field. Visual acuity may be normal initially. **Myopia** (nearsightedness) is the biggest risk factor. (Closed-angle glaucoma risk is farsightedness, or hyperopia.)

Presumptive diagnosis is based mainly on history, but occasionally a portion of the retina appears elevated or folded on ophthalmoscopic exam.

Treatment: This condition requires an **emergent referral** because untreated partial detachment can progress over hours to total retinal detachment with permanent blindness. Small retinal detachments are treated with laser surgery to tack down the area. Larger detachments require scleral buckling (a band around the sclera to restore contact of retina with the wall of the eye), transscleral drainage of fluid, vitrectomy (removal of vitreous), or injection of gas or other fluid into the eye (to tamponade the retina).

Retinal Vascular Occlusion

Retinal Artery Occlusion

Occlusion of the central retinal **artery**—usually embolic—causes sudden, painless, **unilateral** blindness. This is a **true ocular emergency** in which every minute counts. Retinal edema (sparing the relatively thin fovea) creates pallor and the appearance of a “**cherry red spot**” in the macula.

Treatment is directed toward dislodging the embolus and includes **ocular massage** and/or **paracentesis** of the anterior chamber (to lower pressure). While waiting for the ophthalmologist, have the patient get into the Trendelenburg position and breathe into a paper sack. You may massage the affected globe with your index fingers (5 sec pressure, 5 sec no pressure, repeat). Unfortunately, all these temporary measures are rarely effective. Patients subsequently require a thorough systemic evaluation for embolic and carotid disease.

Retinal Vein Thrombosis

Retinal **vein** thrombosis (RVT) causes sudden, painless, **near-total loss** of vision. Causes include hypertension, polycythemia vera, and Waldenström macroglobulinemia. Retinal edema is accompanied by hemorrhage—**not** a cherry red spot.

Diagnosis is made with an ophthalmoscopic exam showing a “blood and thunder” fundus with multiple hemorrhages.

Patients with RVT usually are just observed; however if they have macular edema or neovascularization, refer immediately to ophthalmologist.

Macular Degeneration

Age-related macular degeneration is the leading cause of irreversible **acquired** legal blindness in developed countries. There are 2 types: atrophic (or “dry”) and neovascular (or “wet”). Atrophic is the **most** common.

Risk factors for both types include **smoking** and **low levels** of **zinc** and **antioxidants** in the diet. However, most trials have not shown any reduced risk with vitamin supplementation or antioxidants. One recent trial, however, did show reduced risk with B vitamin supplements. This is being investigated further.

Background: The fovea is responsible for fine (20/20) visual acuity. The fovea and surrounding retina is called the macular area. Although the macula comprises only 2% of the visual field, 25% of the cone photoreceptors are here, and it correlates with 50% of the primary visual area of the brain.

Atrophic age-related macular degeneration causes a gradual loss of central acuity down to 20/400 (peripheral vision is spared). **Neovascular** age-related macular degeneration is somewhat amenable to treatment with laser photocoagulation, photodynamic therapy, and/or intravitreal ranibizumab or bevacizumab.

OPTIC NERVE

Optic Neuritis (ON)

ON is an inflammation of the optic nerve and is a frequent presentation of multiple sclerosis (MS).

ON presents with ocular pain, especially with eye movement. On exam, the optic disc is usually normal **initially**

(“the doctor sees nothing, the patient sees nothing”) and only later develops pallor. Refer the patient to an ophthalmologist. IV glucocorticoids improve vision more quickly, but these are controversial because patients **not** given steroids ultimately regain vision as well. Typically, an MRI is done, looking for evidence of MS.

Ischemic Optic Neuropathy

Ischemic optic neuropathy is the feared complication of giant-cell (temporal) arteritis. Other signs and symptoms are those of polymyalgia rheumatica: malaise, fever, weight loss, muscle aches, jaw claudication, elevated ESR (erythrocyte sedimentation rate). Corticosteroids are started as presumptive treatment even before the diagnostic temporal artery biopsy is done.

VITREOUS HUMOR

Vitreous **degeneration** occurs in all elderly persons. They tend to get bothersome floaters, brief unilateral flashing lights (from the vitreous traction on the retina), and **vitreous detachment** (with a sudden shower of floaters and flashing lights). Vitreous detachment is not dangerous **unless** it damages the retina.

Vitreous **hemorrhage** is a cause of sudden, painless loss of vision. It is caused by either a vitreous detachment **tearing a retinal vessel** or as a result of breakage of the fragile blood vessels in **diabetics** with the **neovascularization** (proliferative diabetic retinopathy).

Any patient with vitreous **detachment** should be referred to an ophthalmologist, who will look for current retinal detachment and also defects that, when repaired, may forestall future retinal detachment. The eye with vitreous hemorrhage must be examined by ultrasound to check for retinal detachment.

CATARACTS

The crystalline lens of the eye is a clear biconvex structure behind the iris and supported by the zonules. The lens is initially pliable and reactive to accommodation. As the lens ages, it gets less pliable and may get less clear. **Any** lens opacity is called a cataract. Cataracts cause a very **gradual, painless, progressive loss of vision**. Treatment is cataract surgery with replacement of the lens.

CRANIAL NERVE DYSFUNCTION

Suspect cranial nerve (CN) involvement in the patient who presents with sudden onset of **painless double vision** (Figure 10-7).

6th CN (abducens; CN VI) supplies the lateral rectus. Paralysis: cannot move the eye laterally.

4th CN (trochlear, CN IV) paralysis: Eye is deviated upward and the head tilted toward the uninvolved side (Bielschowsky sign).

Quick Quiz

- What is the leading cause of acquired legal blindness in the U.S.?
- Optic neuritis may signal the development of what neurologic disorder?
- What is vitreous hemorrhage?
- Know the eye movements associated with the 3rd, 4th, and 6th cranial nerves.

3rd CN (oculomotor, CN III). Motor: 2 branches, superior and inferior. The superior branch supplies the superior rectus and the levator palpebrae superioris (eyelid muscle). The inferior branch innervates the inferior rectus, inferior oblique, and the medial rectus. There is also a parasympathetic component of CN III, which is yet another branch. It results in tonic constriction of the pupil. Complete paralysis of CN III results in an eye that is deviated “down and out” (due to unopposed activity of the superior oblique [CN IV] and lateral rectus [CN VI]), a ptotic eyelid, and a dilated pupil. If the eye is **not** dilated, the patient probably has diabetic vascular disease affecting only the somatic branches.

EYE INJURY

Trauma

Check acuity; inspect anterior chamber for layered blood (hyphema), corneal laceration, subconjunctival hemorrhage, puncture wound, or pupil distortion; use ophthalmoscopy to confirm clear view of retina and no other signs of hemorrhage. If there is pain, instill fluorescein to check for corneal abrasion and evert, inspect, and swab the upper lid, looking for a **foreign body**. Any abnormal finding, except perhaps a small corneal abrasion, requires consultation. Never patch corneal abrasions in contact lens wearers.

Alkali Injury

Alkali injury is a special form of trauma where treatment delay of minutes **can devastate** the eye. Alkali rapidly penetrates the cornea and enters the anterior chamber, where it wreaks havoc. Treatment is immediate, consisting of **profuse irrigation**, with lid eversion to remove any alkali-containing particles. Check pH of tears to confirm that it is normal before discontinuing irrigation. Vessels may be blanched by alkali solution in severe injury, paradoxically creating the appearance of a “white and quiet” eye.

RED EYE

Assessment

The most common cause of a red eye is **conjunctivitis**. Conjunctivitis may be bacterial, viral, or allergic. By far

the most common cause of acute red eye is viral—usually adenovirus. A red eye may also indicate more urgent conditions. Workup should include evaluation of certain key differentiating features—acuity, pain, and photophobia (light sensitivity). Other features to assess are preauricular adenopathy, amount and type of discharge, and the location and amount of redness.

Significant findings:

- 1) Decreased **visual acuity** may indicate a **serious** problem requiring prompt consultation. Check for an afferent pupillary defect (seen more often in serious eye conditions).
- 2) **Photophobia** is a key feature of iridocyclitis (and other more serious conditions), which should be evaluated promptly (within 24 hours) for possible intensive topical steroid treatment.
- 3) **Type of redness**. Bright red confluent blood is seen with subconjunctival hemorrhage. Ciliary flush (red near corneal limbus only in a sun ray-like pattern) suggests iridocyclitis, keratitis, or angle closure. Diffuse conjunctival hyperemia is nonspecific.
- 4) **Pain** is **not** common in typical infectious causes of red eye. In patients who have photophobia, foreign body sensation, and/or vision complaints, consider the more serious conditions of anterior uveitis, keratitis, or acute closed-angle glaucoma.
- 5) **Preauricular adenopathy** (may be tender) is highly suggestive of adenoviral conjunctivitis.
- 6) **Discharge**, if **purulent**, suggests **bacterial** etiology. Clear exudate more likely suggests viral. White, stringy exudate may be allergic, especially if associated with pruritus. If there is no pruritus, it is more likely dry eye (keratoconjunctivitis sicca—see below).

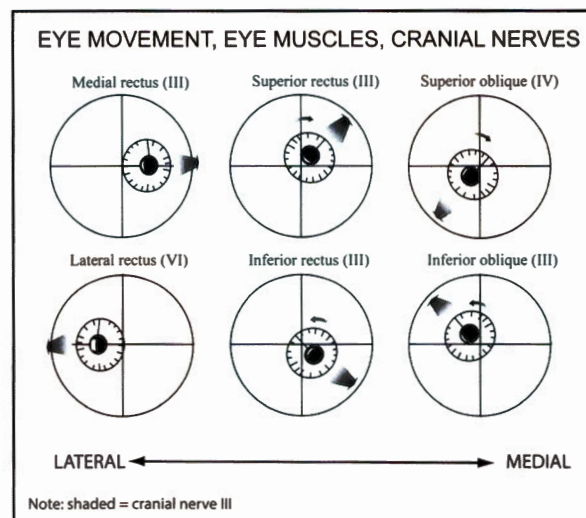


Figure 10-7: Cranial Nerves Associated with Eye Movements

Anterior Uveitis

This is **autoimmune** inflammation of the anterior eye structures. It occurs as a solitary problem but is also seen with many diseases (e.g., spondyloarthropathies, sarcoidosis, lupus, vasculitides). You can make a presumptive diagnosis with symptoms of ocular pain, photophobia, and a ciliary flush with a normal cornea

and normal intraocular pressure. Slit lamp exam reveals inflammatory cells floating in the aqueous humor or deposited on the corneal epithelium. This presentation requires **emergent referral!** Treatment: steroids (to reduce inflammation and scarring) and cycloplegics (to prevent synechiae).

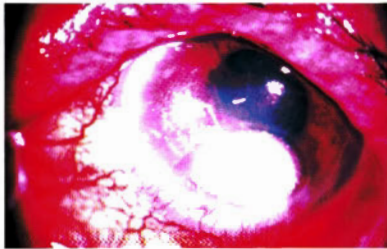


Image 10-1: Corneal Ulcer. Usually caused by improper use of contact lenses. It is especially seen with the extended-wear contact lenses.

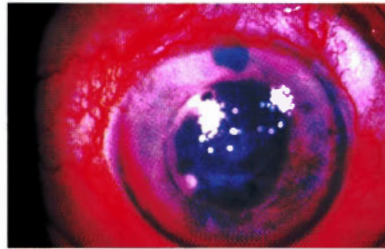


Image 10-2: Proliferative Diabetic Retinopathy: Rubeosis. Blood vessels grow onto the iris. This may cause intractable glaucoma. Also caused by central retinal vein thrombosis.

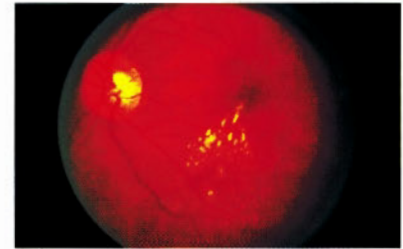


Image 10-3: Hard Exudate as seen in non-diabetic retinopathy. This is caused by leakage of protein and lipids from capillaries. Treatment is photocoagulation of the leaking capillaries.

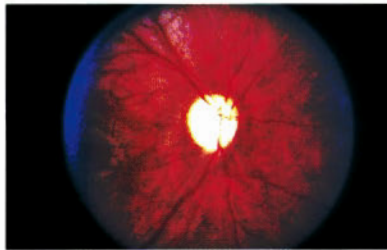


Image 10-4: Optic Atrophy has various causes, including proliferative diabetic retinopathy and central retinal artery occlusion. In older patients, also consider ischemic optic neuropathy.

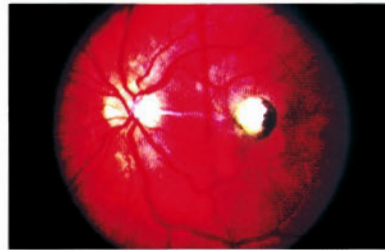


Image 10-5: Toxoplasmosis.

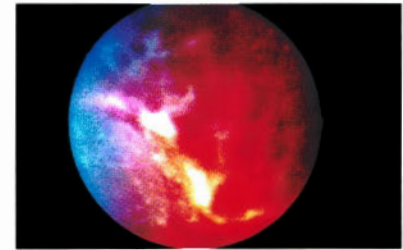


Image 10-6: Proliferative Diabetic Retinopathy. Vitreous hemorrhage.

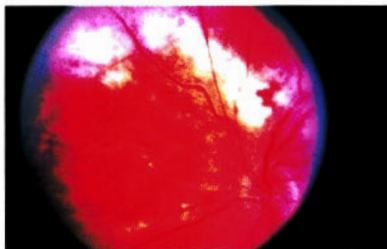


Image 10-7: CMV Retinitis. Especially seen in people with AIDS.



Image 10-8: Arcus Senilis. Common in older patients. In patients < 40 yrs, it may be a sign of a lipid disorder.

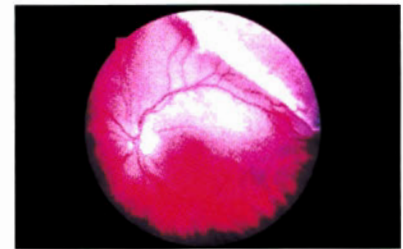


Image 10-9: Retinal Detachment. This usually occurs in very myopic people. It often occurs after a vitreous hemorrhage.

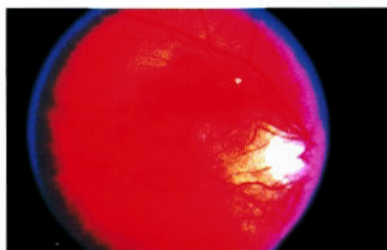


Image 10-10: Branch Retinal Vein Occlusion (BRVO). Main cause is hypertension but also seen with diabetes and with hyperviscosity syndromes. Think of this as exaggerated AV nicking with the artery pinching off the vein.

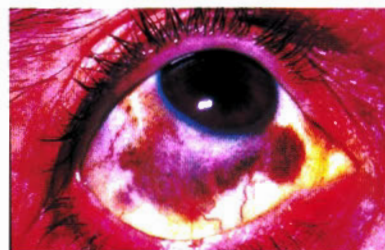


Image 10-11: Heterochromia, Ocular Melanosis. This is a normal finding in darkly pigmented persons. Rarely caused by Fuch's iridocyclitis.

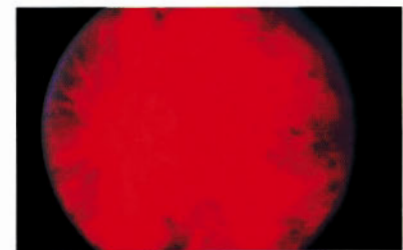


Image 10-12: Central Retinal Vein Thrombosis (CRVO). Same causes as BRVO.

Quick Quiz

- What virus is usually responsible for conjunctivitis?
- A contact lens wearer presents with severe keratitis and says she uses tap water frequently for lens care. What organism should you consider?

Keratoconjunctivitis Sicca (Keratitis)

This is most common in the elderly and in middle-aged women. It may be an early sign of systemic inflammatory disease, including Graves disease, rheumatoid arthritis, and sarcoidosis. Treat most cases with artificial tears (electrolyte solutions, methylcellulose, or other formulations).

Viral Conjunctivitis

Viruses are, by far, the most common cause of red eye. Patients have diffuse conjunctival hyperemia and profuse watery discharge (often with other signs/symptoms of a viral infection). No specific treatment, just practice strict hygiene. Adenovirus is one of the most common etiologies, especially in the summer around swimming pools. It should resolve in 5–7 days.

Bacterial Conjunctivitis

Bacterial conjunctivitis may be caused by staph, strep, *H. influenzae*, *Pseudomonas*, *Moraxella*, or *Neisseria*. Most cases of bacterial conjunctivitis will resolve in 5 days even without treatment; **but we do treat** and follow closely because the patient can develop vision loss.

Red eye with profuse purulent discharge is the typical presentation.

Treat uncomplicated cases with topical erythromycin, sulfa, or polymyxin/trimethoprim (drops or ointment; drops are preferred for adults because vision is blurry for ~ 20 minutes after insertion). Remember: Some patients have sulfa allergy, so worsening conjunctivitis after sulfa treatment may be due to allergy. Reserve quinolones for the more serious cases.

If complicated, obtain cultures, initiate treatment with gatifloxacin or moxifloxacin, **and** refer to an **ophthalmologist**. Aminoglycosides are not used much anymore because they irritate the cornea and cause inflammation after a few days.

Neisseria conjunctivitis (can be gonococcal or meningococcal) is a “hyperacute” (severe conjunctival discharge and redness) conjunctivitis that requires early recognition and **aggressive topical treatment** to prevent progression to corneal perforation. Systemic therapy is also indicated.

Patients who use extended-wear **contact lenses** have an impaired ability to fight conjunctivitis and are at high risk for developing vision-threatening complications. Always consider an ophthalmology referral at presentation if the patient wears lenses.

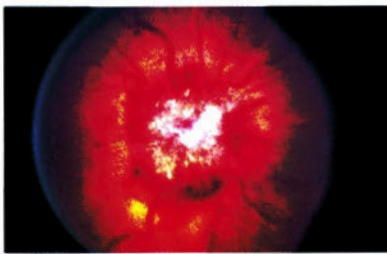


Image 10-13: Papilledema. Seen with increased intracranial pressure. Think of tumor and pseudotumor cerebri. Mimics optic neuritis/papillitis, except papilledema is bilateral.



Image 10-14: Allergic Conjunctivitis. Usually seasonal.

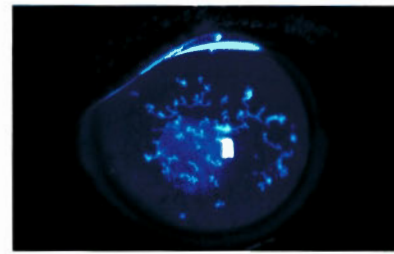


Image 10-15: Herpes Keratitis of the cornea. Frequently recurs.

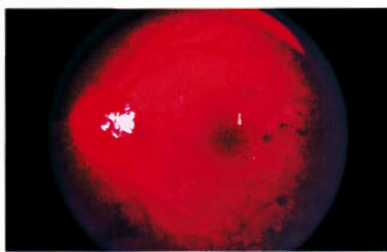


Image 10-16: Proliferative Diabetic Retinopathy with disc neoplasia.



Image 10-17: Pterygium. Associated with exposure to ultraviolet light and dry wind. Seen in farmers, professional golfers, etc.



Image 10-18: Synechiae. This is a possible sequela of iritis (iridocyclitis). 90% of iritis is idiopathic, but it is seen in inflammatory diseases such as viral infections and connective tissue diseases.

Pseudomonas conjunctivitis can progress to **corneal perforation** overnight in these patients. Any contact lens wearer with conjunctivitis should **immediately** discontinue use of the lenses. Start these patients on topical **gatifloxacin** to cover *Pseudomonas* and gram-positives, and refer to an ophthalmologist.

Acanthamoeba is a known cause of infection with lens-wearers, especially if the patient uses tap water for lens cleaning. Usually it progresses rapidly to keratitis.

Infectious Keratitis

Think about **bacterial keratitis** in patients who wear contact lenses and who present with a painful eye that is difficult to keep open. Non-lens-wearers can also get bacterial keratitis, especially if immunosuppressed. Organisms usually responsible: staph, *Pseudomonas*, and pneumococcus.

On exam, the eye is red with a **mucoïd** discharge and a visible **white spot** (corneal opacity) that is easily seen with a penlight. Fluorescein staining shows the area as well.

Treatment includes emergent referral to an ophthalmologist.

Viral keratitis can be caused by **reactivation** of latent herpes simplex. It may present similarly to bacterial conjunctivitis discussed above. Fluorescein staining shows a characteristic **dendritic branching pattern**. Risk factors for reactivation include laser eye treatments and immunosuppression. Diagnosis is purely clinical because most patients have antibodies to HSV, and viral culture takes days. Treatment is with oral or topical antivirals (**but not both**). Know that topical steroids can seriously exacerbate the infection, so do not prescribe any topical steroids for an eye unless you are certain that the underlying diagnosis is **not** herpes keratitis. Some patients have problems with recurrent disease (similar to fever blisters from HSV); these patients can be managed with chronic oral antivirals.

OTHER EYE INFECTIONS

Endophthalmitis

Endophthalmitis (infection inside the eye) can have an ocular (traumatic) or systemic (blood stream seeding) source—and can be bacterial or fungal. The most common presentation is bacterial infection after cataract surgery, and the organism is usually a coagulase-negative *Staphylococcus*. Patients present with decreased visual acuity, hazy cornea, pain, and hypopyon (layering of white cells visible in the anterior chamber.) Refer immediately. The ophthalmologist will do vitrectomy and culture the vitreous fluid; then intraocular antibiotics are injected (vancomycin + [ceftazidime or amikacin]). Systemic antibiotics are added in severe cases, although utility is controversial. It is important

to choose antibiotics that cross the **blood-brain barrier**; otherwise, the drugs will **not** reach the vitreous fluid. Cataract lenses do not have to be removed, unless the infecting organism is a fungus. Remember: If trauma to the orbit is involved, suspect *Bacillus cereus*!

Candida endophthalmitis is seen more commonly because of the widespread use of prolonged intravenous access and cases of fungemia. *Candida* can reach the eye via trauma or bloodstream infection. Bacterial and fungal endophthalmitis present similarly, which is the reason why cultures are of paramount importance in post-surgical patients. Risk factors for candidemia include long-term venous access, neutropenic immunosuppression, long-term broad-spectrum antibiotics, and corticosteroid treatment. Know that injection drug users who dilute drugs (usually heroin) in contaminated lemon juice are at increased risk. Treatment includes removal of the lens and systemic azole antifungal treatment (not amphotericin B because it does not achieve high levels in the eye).

Periorbital and Orbital Cellulitis

Periorbital cellulitis usually is a rapidly progressive **cellulitis** of the periorbital area, which **may** become orbital if not treated. Patients present with warmth, redness, and swelling around the eye. Key physical exam finding is normal extraocular muscle movement without diplopia or pain with eye movement.

If the patient has disconjugate gaze, diplopia, or pain with eye movement, it is probably the result of infection that has moved into the orbital space. This warrants a periorbital CT or MRI, and IV antibiotics with MRSA and strep coverage, such as vancomycin and ceftriaxone.

Chalazion

Chalazion is caused by obstruction of one of the tarsal (meibomian) glands forming a small nodule found in the tarsus under the eyelid. Not a problem **unless** secondary infection occurs. Such infections often require ophthalmologic surgery.

Stye

Stye is an abscess at the base of an eyelid. Treat it with warm compresses and a topical ophthalmologic antibiotic. Occasionally, it will require drainage.

EYE EMERGENCIES — REVIEW

Briefly, here is how to approach ophthalmologic emergencies.

Treat emergently and immediately refer:

- alkali burn,
- trauma,
- orbital cellulitis,
- central retinal artery occlusion,

Quick Quiz

- What is the best way to diagnose an acoustic neuroma?
- A Rinne test is done. The patient can hear the tuning fork more loudly when it is on the bone. What does this mean?
- A Weber test is done on the same patient. He can hear sounds more loudly on the left side. What does this mean?

- angle-closure glaucoma, and
- optic nerve infarction in giant-cell arteritis.

Refer **immediately** without on-site treatment:

- penetrating ocular injury,
- endophthalmitis,
- retinal detachment, and
- keratitis/keratoconjunctivitis.

Refer to be seen within **1–2 days**:

- fetal vein thrombosis,
- optic neuritis, and
- vitreous detachment/hemorrhage.

HEARING LOSS

Hearing loss is conductive, sensorineural, or both.

CONDUCTIVE HEARING LOSS

Conductive hearing loss occurs because something blocks sound from entering the inner ear (e.g., otitis media, eustachian tube blockage, otosclerosis, invasive external otitis, TM perforation, and ceruminosis—or any other impaction of the external canal).

Otosclerosis is an autosomal dominant trait with poor penetrance. It is **much more common** in Caucasians than in African-Americans. 10% of Caucasians develop otosclerosis; 1% become symptomatic.

SENSORINEURAL HEARING LOSS

Sensorineural hearing loss is caused by either cochlear damage or nerve damage (CN VIII). It may be caused by viral infections, ototoxic drugs, meningitis, cochlear otosclerosis, Ménière disease, acoustic neuromas, or aging (presbycusis).

Presbycusis is characterized by bilateral symmetrical sensorineural hearing loss in the frequencies > 2,000 Hz. 1/3 of persons older than 65 years have some form.

Ménière disease is uncommon. Affected patients have recurrent, severe attacks of vertigo that persist for

several hours and often are associated with vomiting and prostration. Patients have **tinnitus**, fullness in the ear, and progressive **hearing loss** (which is frequently one-sided) until deaf, at which time symptoms stop!

Diagnosis is made with the combination of typical clinical symptoms and demonstration of sensorineural hearing loss on audiometry. Treatment of acute episodes is benzodiazepines and antiemetics (**not** meclizine!). Chronic treatment includes **avoidance** of caffeine and salt, with the addition of diuretics if symptoms continue.

Acoustic neuromas (vestibular schwannomas) are benign, very slow-growing tumors of the 8th cranial nerve. Patients usually present with **tinnitus**, unilateral **hearing loss**, and **gait imbalance**. MRI is the diagnostic test of choice. Treatment is radiosurgery or surgical resection.

Acute sensorineural hearing loss should be evaluated and treated immediately. If the patient cannot be seen immediately, he should be put on prednisone (40–80 mg/day) and evaluated as soon as possible. There is suggestion that earlier steroids may allow for a larger percentage to have hearing return to them.

RINNE AND WEBER TESTS

Know how to perform the Rinne and Weber tests to differentiate between conductive and sensorineural hearing loss.

Rinne test (Figure 10-8 and Table 10-13) is based on the observation that air-conducted sound is normally louder than bone conducted. The base of the vibrating 256 Hz (best) tuning fork is placed over the mastoid, and the sound of this bone-conducted hearing is compared to the air-conducted sound the patient hears when the tuning fork is placed next to the ear on the same side. With **no** hearing loss, the **air-conducted** sound is loudest. With **conductive** hearing loss, the **bone** conduction is louder. With **sensorineural** hearing loss, **both** air and bone conduction are decreased, **but** the air conduction is **perceived** as being louder.

Weber test consists of placing the base of a 256 or 512 Hz tuning fork on the middle of the forehead. The patient tells you whether the sound lateralizes to one side or stays in the middle. If the sound is perceived as being in the middle, the patient either has normal hearing or the hearing loss is symmetrical. If the sound lateralizes, there is either a conductive hearing loss in the ipsilateral ear or sensorineural loss in the opposite ear.

You can simulate the Weber test by humming and sticking your finger in one ear (causing a conductive hearing loss). If your hearing is normal, the sound lateralizes to the plugged-up ear.

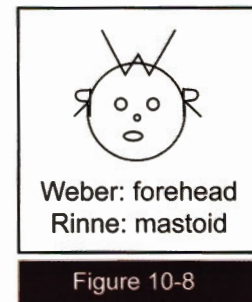


Table 10-13: Diagnosing Conductive vs. Sensorineural Hearing Loss with the Rinne and Weber Tests

Type of Hearing Loss (examples)	Rinne	Weber
	Position A = Air (i.e., fork held next to ear) Position B = Bone (i.e., base on mastoid)	Tuning fork base held at middle of forehead
None	Sound A > B	Sound does not lateralize
Sensorineural loss (in left ear)	Left ear: Both A & B decreased equally so still: Sound A > B	Lateralizes to the right ear
Conductive loss (in left ear)	Left ear: B > A	Lateralizes to the left ear

OFFICE PSYCHIATRY

PSYCHOSOCIAL DISORDERS

Eating Disorders

Anorexia nervosa syndrome usually begins post-puberty and in early adulthood. It almost always occurs in middle-to-upper-class Caucasian women. Anorexia may have a genetic component (concordance in monozygotic twins and increased risk in 1st degree relatives). Currently, data do **not** support any increased incidence of sexual abuse in anorexics.

Diagnosis is clinical. Typically, diagnosis consists of a combination of the following:

- Weight loss has resulted in a weight at least 15% under ideal.
- Patients have a preoccupation with food and have an intense fear of becoming fat.
- There are disturbances in the way body weight and size are experienced. These patients have a distorted self-image and, despite often extreme weight loss, they not only deny thinness but complain of feeling fat. This is a “soft” criterion because many young women have a similar self-perception, although without the weight loss.
- Women have had absence of 3 or more consecutive menstrual cycles.

In advanced cases, patients become emaciated, bradycardic, and hypotensive. Lab studies show anemia, hypokalemia, and hypoalbuminemia. These patients are at risk for sudden death from **ventricular tachyarrhythmias**, especially when refeeding.

Treatment. It is important to establish a supportive advisor role with the patient. Patients are very resistant to psychotherapy, and outpatient supportive care often works just as well as inpatient therapy. Explain the dangers of **starvation**, such as sudden death, and set realistic, short-term goals for weight gain. Acknowledge the patient’s perception and continually reinforce that you will not let her get fat as she gains weight. Treatment is long-term with frequent failures and setbacks. Antidepressants may exacerbate severe anorexia because some are dietary depressants. Cyproheptadine, an appetite stimulant, may help a little. Outcome is very poor in 20–30%. Anorexics are more likely to abuse drugs and have

comorbid anxiety, obsessive-compulsive, and/or personality disorders.

Bulimia is the term used for binge eating of large amounts of food, followed by purging—either with vomiting or with laxatives. It may be a variant of anorexia nervosa, and many bulimia patients have a history of anorexia in their past. Bulimia patients are usually 20–30 years old (older than anorexia patients). These patients are usually **not** < 85% of ideal weight.

Diagnosis of bulimia is clinical. Typical symptoms of bulimia:

- Recurrent episodes of binge eating—at least 2 per week for at least 3 months
- Sense of lack of control over eating behavior
- Overly concerned with body weight and shape
- Regular use of self-induced vomiting, laxatives, dieting, fasting, and vigorous exercise to prevent weight gain

Physical exam may show erosive skin lesions on the fingers where the teeth cause injury during attempts to induce vomiting. **Dental erosions** and an increase in the size of the salivary gland are also seen. The most common **lab abnormalities** are hypokalemia and metabolic alkalosis from vomiting and laxative use. Think about bulimia in **young** women presenting with a Mallory-Weiss tear or severe GERD.

Treatment is again supportive, with the focus on slowly decreasing the amount of food eaten and decreasing the frequency of binge-eating episodes. Treatment, as with anorexia, is long-term, with frequent failures and setbacks. Antidepressants may help.

Anxiety Disorders

Anxiety disorders are classified in 2 ways:

- 1) Generalized anxiety disorder, which is chronic and low-grade
- 2) Panic disorder, with brief and dramatic panic attacks

Generalized anxiety disorder. DSM-IV diagnostic criteria include: anxiety/worry about several activities or events that is more than what is reasonable for the events for ≥ 6 months. **Generalized** anxiety disorder is associated with substance abuse and other psychiatric diagnoses:

Quick Quiz

- A young woman is brought in by her husband for weight loss and lack of menses for 6 months. What diagnosis should you consider?
- How does anorexia nervosa differ from bulimia?
- Describe a patient with neuroleptic malignant syndrome.

obsessive-compulsive disorder, depression, panic disorder, and social phobias. Somatic complaints are common (fatigue, memory problems, tension, inability to sleep).

Treat with **behavioral** therapy. Know that several brief encouraging follow-up visits to a primary care physician has the same effect as prescribing benzodiazepines. Patients who require more than behavior therapy can be treated with SSRIs +/- benzodiazepines (BDZs). Abuse of BDZs is very low in this patient population. Buspirone is useful as a BDZ substitute. Chronic treatment is usually required.

Panic disorder is diagnosed when 4 attacks have occurred within 1 month, or 1 or more attacks are followed by 1 month of intense fear of another attack. These patients often have phobic avoidances of places or situations associated with attacks. Secondary major depression is a common complication. Treatment of panic disorder is usually with **SSRIs and anxiolytics**, such as benzodiazepines or buspirone HCl. The optimal treatment is an **SSRI**, with only short-term use of **benzodiazepine**. Psychotherapy may have some benefit. Longer-acting benzodiazepines (e.g., clonazepam) are preferred over alprazolam.

Bipolar Disorder

Bipolar disorder may present as **solely** manic or hypomanic (mild manic) episodes—the patient may never have had a depressive episode. Most manic patients are euphoric and have inflated self-esteem, decreased need for sleep, and pressured speech. Hypersexuality is common, as is overspending. Some patients are just irritable, possibly also paranoid—this is termed dysphoric mania. Psychotic symptoms are common during manic episodes. The depression is identical to common depression. Lithium, valproic acid, and carbamazepine are effective for most cases. Sometimes, antipsychotics are used in patients who have psychotic features.

The atypical antipsychotics (e.g., olanzapine) do not have the side effects associated with haloperidol; but the atypical drugs are associated with weight gain, diabetes, and hyperlipidemia. **Know that many of the antiepileptic drugs are associated with increased risk of suicide. Also know that thiazide diuretics, ACE-inhibitors, and NSAIDs increase the lithium level.** Refractory bipolar disorder is often treated with electroconvulsive therapy.

Depression

Depression is discussed briefly in the Geriatrics section (see [page 10-16](#)). Of course, this does not mean it occurs only in the elderly, but the general population has the same treatment options as the elderly.

For mild-to-moderate depression the current guidelines recommend psychotherapy and/or medications for an initial 12-week period. If psychotherapy is tried alone and there is no response, then definitely begin medications. After you start meds, the guidelines say to monitor the patient every 1–2 weeks by phone or office visit for the initial 8 weeks. You expect a 56% response rate at 2 weeks, 81% at 4 weeks, and 90% at 6 weeks. If there is no response at 8–12 weeks on maximum doses of the chosen medication, switch to a different drug or augment with bupropion or buspirone. Thyroid augmentation is controversial and not included in current guidelines. Treat for 6–9 months for initial therapy, with a 2–4 week taper after improvement.

Medication Complications

Neuroleptic malignant syndrome (NMS) is an idiosyncratic response to potent neuroleptics, resulting in autonomic dysfunction, extrapyramidal symptoms, and high fever. The fever may reach 106° F. The neuroleptics most commonly involved are **haloperidol**, **piperazine phenothiazines**, and **thiothixene**. NMS is thought to be due to a depletion of dopamine. It persists for up to **10 days** after the drug is stopped. Treatment is to **stop** the causative drug and cool down the patient. Give oral dopamine agonists also to counteract the depletion. **Bromocriptine** is the drug of choice, but you may also use **amantadine** and **dantrolene**.

Serotonin syndrome (SS). One of the functions of serotonin in the brain is to modulate body temperature. Serotonin drugs can cause derangement in thermoregulation—a condition termed “serotonin syndrome.” Think about it in patients who are on at least 1 serotonin drug, but it more often occurs in patients on 2 or more serotonergic drugs. Onset is usually within 6 hours of starting the new or additional drug. Serotonin syndrome can have the presentation of SSRI overdose.

Clinical presentation is anxiety, disorientation, sweating, tachycardia, hypertension, vomiting, and diarrhea. Hyperthermia can be marked. Exam may show rigidity, hyperreflexia, and tremors. This condition looks like neuroleptic malignant syndrome, toxicity from anticholinergics, or overdose of sympathomimetics. Labs may show metabolic acidosis and evidence of rhabdomyolysis.

Treat by discontinuing the serotonergic drug and giving supportive care, including cardiac monitoring. BDZs are helpful for the anxiety and tachycardia. The syndrome usually resolves in 24 hours. The hyperthermia often results from muscle rigidity; so, very hyperthermic

patients usually require intubation and paralysis. Cyproheptadine is a serotonin antagonist that is given in severe cases.

Differentiating NMS and SS based on symptoms is difficult because they present similarly with autonomic changes, hyperthermia, and mental changes. It is important to know that blood tests easily distinguish between them. **NMS** has increased **CK, LDH, AST** (SGOT), and **WBCs** along with a **low serum iron**. Serotonin syndrome typically has normal labs.

SSRI discontinuation syndrome. It is very important to slowly titrate patients off SSRIs. It is generally done over several months but some patients require much longer. If done too quickly, patients can develop light-headedness, vertigo, **shock-like paresthesias**, visual symptoms, anxiety, insomnia, and gastrointestinal symptoms (N/V/D). Diagnosis is usually easy with the history of recent SSRI dosage decrease. Treatment is to boost the drug a little and, once stable, restart the tapering at a slower pace.

GENETICS

Histocompatibility antigens are the antigens involved in graft rejection. Many of the histocompatibility genes are closely grouped on **chromosome 6**, and this area is called the Major Histocompatibility Complex (MHC). The human MHC is termed HLA.

There are 3 classes of antigens found on cells that are associated with the HLA. Again, **all** the HLA genes are on chromosome 6.

Class I HLA antigens: All have the same molecular weight. These antigens are produced by the HLA-A, HLA-B, and HLA-C regions on chromosome 6. These antigens are on most body cells **except** RBCs.

Class II HLA antigens are in the HLA-D region.

Class III HLA antigens are formed in the HLA-B-D region. They consist of 3 complement component structures.

General review of transcription and translation: The DNA has **coding** sequences called **exons**, separated by very small **non-coding** sequences called **introns**. There is a 1:1 ratio of introns:exons. E.g., the gene for 1 small protein may consist of 20 of each, with 95% of the sequence being the introns. The full gene (introns + exons) is transcribed by DNA dependent RNA polymerase into RNA. The introns are then spliced out of the RNA before it leaves the nucleus, thereby forming the messenger RNA (mRNA). The mRNA is then translated into protein: Each 3-base sequence comprises a **codon**, which determines the amino acid that will be attached when it is translated.

Point mutations are a change to a single base, and can result in either a **missense** or a **nonsense** mutation.

Missense mutation is when a point mutation causes a different amino acid to be produced, **as in SS** (valine is substituted for glutamic acid). Nonsense mutation produces a **stop** codon, which stops the translation.

Insertion and deletion mutations: These cause a “frame shift,” which causes an abnormal protein from that point to the end.

Splicing mutations result from a point mutation at the area defining the junction between the intron and the exon. This results in dysfunctional proteins. **Beta thalassemias** often are caused by splicing mutations.

Clues for autosomal dominant disease:

- **Vertical** transmission (involving several generations).
- Risk to each child of affected individual is **50%**.
- Male-male transmission is observed.
- Normal parents don’t transmit the trait (unless a new mutation occurs).

Clues for X-linked inheritance:

- Inheritance of trait is father to daughter—**all** daughters of affected males are carriers; no sons of the father are affected.
- If mother is a “carrier,” she has a **50% risk** of transmitting the gene to her sons, and each son with a resulting abnormal X chromosome would therefore be affected. A “carrier” mother has a 50% risk of transmitting the gene to her daughters. If a daughter receives the abnormal X chromosome, she is usually **unaffected** but becomes a potential carrier to future generations.

Acquired chromosomal abnormalities: A viral gene that can transform DNA is called a viral **oncogene**. The human chromosomes also contain genes that are associated with malignancy, called cellular oncogenes or **proto-oncogenes**. These proto-oncogenes probably have something to do with embryonal development and are otherwise silent, but, with certain chromosomal rearrangement, they become active. In both Philadelphia chromosome and Burkitt’s, the proto-oncogene becomes active by an **acquired reciprocal translocation**.

The Philadelphia (Ph1) chromosome t(9;22) was the **first** chromosomal abnormality found to be associated with malignancy (first found in CML). The switch causes the “c-ABL” proto-oncogene to be moved from chromosome 9 to 22.

Burkitt lymphoma and its leukemic analog, ALL (FAB type 3), have a reciprocal translocation that switches the proto-oncogene “c-MYC” on **chromosome 8** to chromosome 14, 22, or 2: i.e., t(8;14), t(8;22), or t(8;2). Chromosome 14 has the heavy chain locus. The lambda light chain locus is on chromosome 22, and the kappa light chain locus is on chromosome 2.

Quick Quiz

- Define the Philadelphia chromosome yet again.
- Know [Table 10-14!](#)
- Are ACE inhibitors safe in pregnancy?
- During what trimester is metronidazole contraindicated?

Most leukemia and lymphoma patients have a chromosomal abnormality. Solid tumors **rarely** have abnormal chromosomes.

WOMEN'S HEALTH

OFFICE OBSTETRICS

The following is a compilation of everything written on pregnancy in these Core Curriculum books—plus more. This compilation makes it easier to review pregnancy as a specific topic. Because this is a very important topic, consider the entire section highlighted!

Drugs in Pregnancy

Medications in pregnancy are categorized as follows:

C = some adverse effect in animal studies or no controlled studies in women. Use only if potential benefit outweighs potential risk to fetus.

D = positive evidence of human fetal risk, but may be acceptable despite the risk (e.g., life-threatening illness)

X = causes fetal abnormalities. Do not use.

Also know [Table 10-14](#): Most Asked-About Drugs in Pregnancy.

♦ Gastroenterology

Endoscopic Workup

Esophagogastroduodenoscopy (EGD) is the option of choice for workup of many GI diseases during pregnancy in order to limit or preclude the use of radiation.

Endoscopic ultrasonography (EUS) is normally used in evaluating pancreatic diseases. It is also used in biliary duct disease when an ERCP would normally be used but is contraindicated (e.g., gallstone pancreatitis and pregnancy).

GE Reflux Disease

LES pressure is **decreased** by progesterone (pregnancy increases GE reflux) as well as chocolate, smoking, and some medications, especially those with anticholinergic properties. Avoid bismuth subsalicylate due to the salicylate exposure.

Crohn Disease Meds

FDA risk category B (no evidence of risk in humans):

- Metronidazole (although generally contraindicated in **1st trimester**)
- Prednisone
- Sulfasalazine
- Mesalamine

Olsalazine is FDA risk category C (risk cannot be ruled out).

Constipation

The altered progesterone and estrogen levels are the probable cause of constipation in **pregnancy**.

Pancreatitis

Cullen sign is also seen with intra-peritoneal bleeding (esp. ruptured ectopic pregnancy), and Turner sign is seen with other causes of retroperitoneal bleeding.

Liver Disease

Unlike hepatitis A, hepatitis E carries a **very high risk** for fulminant hepatitis in the **3rd** trimester of pregnancy—with a 20% fatality rate.

1st trimester: Hyperemesis gravidarum can cause N/V, volume depletion, and mild increase in AST and ALT.

2nd trimester: best time for surgery for severely symptomatic **gallstone** patients.

3rd trimester:

- Remember that hepatitis E can cause fulminant hepatitis in the **3rd** trimester of pregnancy—with a 20% fatality rate. The scenario presented may be

Table 10-14: Most Asked-About Drugs in Pregnancy

Dangerous (do not use)	Relatively safe drugs
ACE inhibitors, ARBs, nitroprusside	Clonidine, labetalol, calcium-channel blockers in trials, digoxin, verapamil, procainamide
Ciprofloxacin, doxycycline, tetracycline, metronidazole in 1 st trimester, podophyllin	Sulfasalazine, beta-lactams, erythromycin, azithromycin, amphotericin B
Most aminoglycosides	Gentamicin
I ¹³¹ , methimazole	PTU
Most antihistamines	Chlorpheniramine
Warfarin	Heparin

a pregnant women traveling to Southeast Asia and contracts hepatitis E (fecal-oral transmission like hepatitis A).

- Fatty liver of pregnancy is a very serious condition in which there is **microvesicular** fat deposition in the liver (as in Reye syndrome), with only modest elevation of AST/ALT/Bili. It occurs in the 3rd trimester and is associated with encephalopathy, hypoglycemia (again like Reye syndrome), preeclampsia, pancreatitis, DIC, and renal failure. Early delivery is required.
- Intrahepatic cholestasis of pregnancy causes **itching** and increased alk phos, bili, AST, and ALT.

♦ Pulmonary Medicine

Asthma Treatment

Budesonide is **preferred** in pregnancy, but all ICS may be used.

Tuberculosis Treatment

Do **not** use PZA in pregnancy because it causes birth defects. Streptomycin is also avoided.

Pregnancy is generally considered an **absolute** contraindication for warfarin.

♦ Cardiology

Normal Findings in Pregnant Women

S₃: An S₃ is normal and commonly heard in children and in persons with high cardiac output, such as pregnant women. S₃ is virtually **always** abnormal in non-pregnant patients > 40 years old.

Most pregnant women experience some pedal edema. Flow murmurs (and S₃ gallops) are also common, and the jugular venous pressure increases.

Abnormal Cardiac Issues in Pregnancy

Absolute contraindications to pregnancy include **pulmonary arterial hypertension** and **Eisenmenger** syndrome. In secundum ASD, aortic stenosis, and dilated cardiomyopathy, the patient must be closely watched. In aortic stenosis and dilated cardiomyopathy, patients are usually kept at bedrest. Secundum ASD patients are usually not at risk for cardiac decompensation, **unless** they develop **atrial fibrillation**. Cyanotic heart disease is the worst risk.

Atrial fibrillation: Like secundum ASD above, the initial presentation of mitral stenosis (MS) in a pregnant patient may be new-onset atrial fibrillation and pulmonary edema. The increased blood volume in pregnancy can cause a precipitous exacerbation of MS—so consider treating all pregnant MS patients with digoxin.

So remember that a pregnant patient presenting with new-onset atrial fibrillation and pulmonary edema

indicates a need to rule out both **mitral stenosis** and **secundum ASD**.

A maternal **rubella** infection during pregnancy is a common cause of patent ductus arteriosus (PDA), supra-aortic stenosis, branch pulmonary stenosis (“peripheral PS”), and other congenital cardiac defects.

Aortic dissection: 3rd trimester of pregnancy, systemic hypertension, cystic medial necrosis, bicuspid aortic valve, and coarctation of the aorta are predisposing factors.

Valve surgery: Porcine valves (vs. mechanical valves) are often given to women of childbearing age to **preclude** the use of anticoagulants during pregnancy.

In patients without prosthetic valves, warfarin is contraindicated in pregnancy due to its teratogenic effects. It is **absolutely** contraindicated in the 1st trimester, although, to be safe, most physicians do not give it at all during pregnancy. There is recent controversy about use of LMWH versus warfarin for anticoagulation with prosthetic valves during pregnancy. Most now recommend discussion with the woman about the risks and benefits to her and the unborn child of using warfarin (less risk of thrombosis for her; increased risk of defects for the infant) vs. LMWH (increased risk of thrombosis for the mother; decreased risk of defects for the infant).

Heparin, LMWH, digoxin, quinidine, propranolol, calcium channel blockers, and electrical cardioversion are **not** contraindicated. Although heparin is not contraindicated, it **does** cause increased morbidity and mortality in mother and child. (Long-term use of heparin in pregnancy is associated with osteoporosis, and many recommend increased RDAs for calcium.)

In 2008, the American College of Cardiology wrote a guideline specifically looking at cardiology issues in all women. The main items to know:

- Hormone therapy should **not** be used as primary or secondary prevention of cardiac disease.
- Antioxidants should **not** be used as primary or secondary prevention of cardiac disease.
- Folic acid should **not** be used for prevention of cardiac disease.
- Aspirin in **healthy** women < age 65 years is **not** recommended to prevent MI (but **is** recommended for ≥ 65 to prevent **stroke**).

♦ Infectious Disease

Bacterial Infections

UTIs: *Streptococcus agalactiae* and *E. coli*. Treat with ampicillin, cephalexin, or nitrofurantoin. Ciprofloxacin is **not** given to pregnant women.

Listeria monocytogenes infections are associated with **decreased** cellular immunity syndromes like AIDS, lymphoma, and leukemia, but they are also seen in neonates,

Quick Quiz

- A pregnant woman has a DVT. What commonly used anticoagulant is contraindicated?
- Is an S₃ gallop normal in pregnant women?
- What do you have to rule out in a pregnant patient who presents with new-onset atrial fibrillation and pulmonary edema?
- Is electrical cardioversion possible during pregnancy?
- Should asymptomatic bacteriuria in a pregnant woman be treated?
- What is the problem with rubella being acquired in the 1st trimester?
- What is the maternal-to-fetal transmission rate of HIV without ART? With ART?

the elderly, and **pregnant** women. The most common presentation is in the 3rd trimester and presents as a flu-like illness and is picked up by blood culture. Also suspect this in a pregnant woman with a **UTI** and **negative** urine culture.

Streptococcus agalactiae (group B) is also a cause of postpartum endometritis and bacteremia. So suspect this in any woman who develops a **postpartum fever**!

Approximately 5% of pregnant women have *Chlamydia trachomatis* in their genital tracts; antibiotic ointment in infants' eyes at birth does **not** prevent this conjunctivitis. (This ointment is given only for GC conjunctivitis.)

Gonorrhea is more likely to disseminate in pregnant women. The newborn will be at risk for GC conjunctivitis.

Asymptomatic bacteriuria **should** be treated in **pregnant** women (1/3 go on to pyelonephritis!), **neutropenic** patients, and **transplant** patients.

Syphilis is often **asymptomatic** in pregnant women.

Parasitic Diseases

Toxoplasma gondii is serious in the immunocompetent **only** if acquired during **pregnancy**, when it can cause congenital toxoplasmosis (resulting in mental retardation and chorioretinitis). The fetus is more likely to have a congenital infection if the disease is acquired later in pregnancy (15% first trimester; 70% last trimester). Previous infection with toxoplasmosis before pregnancy is generally not a concern in pregnancy.

Viral Infections

Viruses with the greatest teratogenic potential are CMV, varicella zoster, herpes simplex, and rubella. This is especially true if acquired in the 1st trimester.

CMV is **ubiquitous** and the most common cause of **congenital** viral infection. 1–2% of all newborns have the infection *in utero*, but only a few have any abnormalities. These abnormalities, which range from mild neurologic problems to microcephaly, usually occur in mothers with a primary CMV infection.

Rubella is **German measles** (ssRNA virus). If it is acquired by a pregnant patient in the 1st trimester, there is an 80% chance that the baby will have congenital defects—usually severe. Defects include cataracts, heart problems, mental retardation, and fetal death. It is diagnosed in the mother by the hemagglutination-inhibition test. If this test is negative in a newly exposed pregnant patient, repeat it in 3 weeks (after incubation period) before making any decisions. If it is then positive, a therapeutic abortion should be considered. You can diagnose rubella prenatally by finding rubella **IgM** antibody in fetal blood. Immune globulin will **not** prevent the infection, but it **may** give some fetal protection in the patient who declines therapeutic abortion.

Varicella-zoster infection has a **slight** risk of causing congenital defects. The pregnant woman with chicken pox has a 10% chance of developing severe pneumonia.

HIV: There is a mother-to-fetus transmission risk of **30%**. This is reduced to < 1% with 3-drug antiretroviral therapy (ART). So ensure that all pregnant women with HIV receive ART.

Fungal Infections

High dose (400–800 mg/day) fluconazole is now contraindicated in pregnancy (Category D) because of associated abnormalities of the cranium, face, bones, and heart. Single, low-dose fluconazole (150 mg) to treat yeast infection remains Category C.

◆ Nephrology

During **pregnancy**, there is **increased** calcium absorption and excretion because the 1,25-(OH)₂-D is > 2x normal. Even so, frequency of renal stones is the same as in the non-pregnant patient. The urinary tract of the pregnant patient is dilated and, if stones do develop, most pass easily!

There are 4 categories of HTN in pregnancy:

- 1) Chronic HTN: preexisting HTN or HTN before 20th week of gestation
- 2) Preeclampsia: HTN + proteinuria after 20th week of gestation in woman with no history of HTN
- 3) Preeclampsia that complicates chronic hypertension: worsening HTN + proteinuria after 20th week of gestation in a woman with history of controlled, chronic HTN
- 4) Gestational HTN: occurs after 20th week and has **no** proteinuria

The Joint National Committee (JNC) 7 report's stages of HTN do not apply in pregnancy. HTN in pregnancy is defined as mild if BP is 140–159/90–109 and severe if SBP $\geq$ 160/110.

Eclampsia is defined as grand mal seizures in a woman with preeclampsia or gestational HTN.

Preeclampsia (or pregnancy-induced hypertension) more commonly occurs in primigravidas, usually in the 3rd trimester, and resolves after delivery. It is defined as [SBP $>$ 140 or DBP $>$ 90] and proteinuria $>$ 300 mg in 24 hours in a pregnant woman $>$ 20-weeks gestation. The elevated blood pressure must be sustained with at least 2 readings at least 6 hours apart.

Preeclampsia may be symptomatic or asymptomatic (both have HTN and proteinuria). Symptoms of preeclampsia can be mild (headache, vision changes) or severe (seizures, low platelets, stroke or intracerebral hemorrhage, pulmonary edema, hepatic and/or renal failure, and placental abruption). HELLP syndrome is preeclampsia with **elevated** liver enzymes, **low** platelets, and **microangiopathic** hemolytic anemia.

Treat hypertension in pregnancy (regardless of category) to prevent stroke—treatment of the BP does **not** affect the outcome of preeclampsia (weird ... but true). Know that pregnant women with hypertension are at risk for adverse fetal outcomes if blood pressure is driven too low. This is one patient group in whom we actually have **higher BP goals**, not lower! Each 10 mmHg reduction in SBP is associated with a reduction in fetal birthweight.

For women with preeclampsia, recommendations are to start treatment if:

- 1) Symptoms are present, **or**
- 2) Asymptomatic women when SBP $\geq$ 150 or DBP $\geq$ 95 (although these specific numbers are controversial), with a target BP goal of $<$ 130–150/80–100 mmHg

Bedrest is still recommended for asymptomatic or mild preeclampsia (especially if before 34-weeks gestation), although there are no clinical trials to suggest it affects outcome. For severe, symptomatic preeclampsia, definitive treatment is delivery. Ultimately, care providers walk a fine line between delivering a baby too early to relieve preeclampsia and allowing for longer gestational development.

Women with controlled, chronic HTN (BP $<$ 120/80) are taken **off** BP meds, with frequent BP and symptom monitoring. Meds are reinstituted for same BP as mentioned above for preeclampsia (SBP $\geq$ 150 or DBP $\geq$ 95), with target of $<$ 130–150/80–100 mmHg.

Any pregnancy complicated by malignant HTN or severe, symptomatic preeclampsia is treated with parenteral antihypertensives—labetalol is the preferred drug. Hydralazine and CCBs are also sometimes used, but there are less data for these drugs. Know that the

following antihypertensives are **contraindicated**: ACEIs/ARBs (teratogenic), renin inhibitors (teratogenic), and nitroprusside (cyanide poisoning in the baby).

Oral agents used to treat chronic, asymptomatic preeclampsia, gestational hypertension, and chronic hypertension in pregnancy include labetalol (other beta-blockers have less desirable effects, so labetalol is preferred), methyldopa, extended-release nifedipine, and thiazide diuretics (but watch for signs/symptoms of volume contraction).

Be aware that eclampsia can **definitely** occur postpartum, although rarely. A woman who presents hypertensive with generalized seizures within 12 weeks after delivery should be considered eclamptic.

SLE with lupus nephritis. If the disease has been in remission, there is a 90% chance of a successful pregnancy. If it **flares** up during pregnancy, however, 25% of the fetuses die, usually from the lupus anticoagulant antibody causing thrombotic events.

Pregnancy and chronic renal failure. If the creatinine is $<$ 2 and the patient with chronic kidney disease is not hypertensive, there is **not** an increased risk of abortion or malformation, and there is **no** increase in the rate of progression of the renal disease. There **is** an increased risk of pregnancy-induced hypertension.

As renal failure progresses, chance of pregnancy **decreases**. Dialysis patients **rarely** become pregnant. In stable renal **transplant** patients, the outcome of pregnancy is usually **great**!

◆ Endocrinology

The Serum Osmostat

The threshold set point is decreased (ADH is released at a lower osmolality) by pregnancy and pre-menses; the set point is increased by hypervolemia, acute hypertension, and corticosteroids.

Prolactin Levels

Estrogen directly **inhibits** dopamine outflow, so **elevated** PRL levels can also be seen in pregnancy and in patients taking estrogen.

Pituitary Adenoma

About 1/3 of pituitary macroadenomas, some of which cause increased prolactin levels, **enlarge** during pregnancy. If the tumor enlarges enough to cause symptoms, **bromocriptine** can be restarted (or surgery, if vision is threatened). Bromocriptine is almost assuredly safe in pregnancy, and cabergoline is probably also safe (less experience). But neither drug is FDA-approved for this use.

Quick Quiz

- How do you make the diagnosis of preeclampsia?
- What are the symptoms that may occur with preeclampsia?
- A pregnant woman has Graves disease. What can you do to treat her?
- What is a common mineral deficiency in pregnant women who have not had prenatal care?

Thyroid Disease

One can usually safely give I^{131} treatment to hyperthyroid patients, but it is **not safe** to give it to either **pregnant** patients or patients with **severe** hyperthyroidism.

Always treat pregnant hypothyroid patients and follow their TSH levels during pregnancy—because their requirements will increase (dose needs to be **increased** to 50% more than the pre-pregnancy dose). Failure to treat maternal hypothyroidism during pregnancy can adversely affect the baby.

Treating Graves Disease in Pregnancy

Surgery may be indicated in pregnancy, in patients with an associated cold nodule or relapse after radiation, and in some young patients with a large goiter.

Working Up Amenorrhea

Initial labs should include a pregnancy test and FSH + LH.

Pregnancy in Patients with Polycystic Ovaries

Treatment of PCOS first includes education about weight loss and then is dependent on the **degree** of hyperandrogenism and **whether** pregnancy is desired:

- **No hirsutism** and **no desire** for pregnancy: Prescribe medroxyprogesterone every 1–3 months to induce withdrawal bleeding and to protect the endometrium from hyperplasia.
- **Hirsute** and **no desire** for pregnancy: Prescribe combined estrogen-progesterone oral contraceptives; hirsute symptoms can also be ameliorated with depilatories/shaving. An insulin sensitizer, such as metformin or a thiazolidinedione, may also confer a very modest additional benefit on hirsutism.
- **Hirsute** and **desires** pregnancy: Induce ovulation with clomiphene with or without metformin.

Pregnancy also increases insulin resistance due to placental hormones.

Gestational Diabetes

With pregnancy, strict control even before conception is important. Maintain FPG < 100 mg/dL and A1c < 7%. Before conception, control of blood glucose reduces fetal malformation, and, during pregnancy, it reduces miscarriages, fetal anomalies/death, and newborn problems. Tight glycemic control decreases the risk of macrosomia (birth weight $\geq$ 9–10 lb) and shoulder dystocia in the newborn.

During pregnancy, insulin requirements increase based on gestational age of the fetus. This increased requirement is gone **immediately** after delivery, so anticipate a reduction in insulin dosage of at least **50%** postpartum and observe the patient carefully the day after delivery.

Know: These medications commonly employed in diabetic management are **contraindicated** in pregnancy:

- **Statins** and **ACEIs** are category **X** and should be discontinued **before** pregnancy.
- ARBs are category C (1st trimester) and D (later trimesters).
- Many oral hypoglycemics are category C.

♦ Hematology / Oncology

Fe deficiency is commonly seen in pregnant women who have had no prenatal care.

Early menarche, late menopause, and late first pregnancy are associated with breast cancer.

♦ Neurology

Migraine

Because of risk of inducing ischemia, do **not** use triptans in pregnancy.

Pseudotumor Cerebri

It usually occurs in premenopausal obese women (90%) and may occur during pregnancy.

Seizures During Pregnancy

The background risk for birth defects is 2–3%. The goal of treatment during pregnancy is to **control** the seizures—uncontrolled seizures can cause placental abruption and early labor and premature delivery. When the risk of teratogenicity is compared to the problems that seizures cause during pregnancy, the risk of uncontrolled seizures is **greater**!

Maintain a pregnant woman on **monotherapy** and at the **lowest dose** of medication possible; risk of malformations increases as each drug is added.

There is **no** “safe” antiepileptic drug (AED), but valproate is more likely to cause neural tube defects than other commonly used antiepileptics.

The teratogenic risk of AEDs is **decreased** by **folic acid**, and **all** women of childbearing age on antiepileptic drugs should take folate daily—some recommend 4 mg/day for these high-risk patients.

Physicians generally give prophylactic **vitamin K** during the last **month** of pregnancy in patients on AEDs. This is based on reports indicating increased bleeding in patients on AEDs. Most recent guidelines (AAN AES 2009) say there is not enough evidence to recommend for or against use of prophylactic vitamin K.

Carpal Tunnel (CTS)

Know that pregnancy can cause an **acute** presentation of CTS that typically improves after delivery. Splints are the best treatment for this patient group.

♦ Rheumatology

Methotrexate use: Preexisting renal or liver disease (e.g., HBV, HCV, **alcohol abuse**) and pregnancy are definite contraindications.

Leflunomide use: contraindicated in pregnancy. **Pregnancy** and menstruation are predisposing factors to disseminated gonorrhea.

SLE and Pregnancy

SSA (Ro)/SSB (La) antibodies are associated with neonatal lupus and congenital heart block. General internists **need to know about this risk** when counseling women with lupus about pregnancy.

Lupus patients have a **higher** incidence of failed pregnancies. Risk of pregnancy complications (flare or fetal problems) is much greater if disease is **active** (especially renal manifestations) **or** if the mother has anti-ds-DNA or antiphospholipid antibodies (APS). Pregnant women with APS and a history of recurrent miscarriages can be treated with heparins (low-molecular-weight or unfractionated) plus low-dose aspirin—to decrease incidence of miscarriage. Heart block starting in the 3rd trimester can be seen in babies of mothers with SLE who have SSA (Ro)/SSB (La) antibodies.

If a SLE patient wishes to become pregnant and has had a recent lupus flare, **continue** the glucocorticoids. Measure baseline complements, anti-ds-DNA, SSA/SSB, and a 24-hour urine protein before or very early in the pregnancy. Flares during pregnancy are managed with corticosteroids. **Refer** pregnant women with systemic lupus to a high-risk obstetrician (and pediatric cardiologist, if appropriate).

Avascular Necrosis of the Hip

Other causes include sickle cell disease, pregnancy, HIV/AIDS, Gaucher disease, and hypercoagulable states.

♦ Dermatology

Treatment of Acne

Comedonal (noninflammatory) acne: **Topical retinoids** are drugs of choice for **comedonal** acne. These include adapalene, tretinoin, and tazarotene. However, tazarotene (Tazorac®, Avage®) is **contraindicated** in pregnancy (category X), and topical tretinoin has been associated with fetal defects (category C)! Recommended agents include oral/topical erythromycin, topical clindamycin or azelaic acid. Topical benzoyl peroxide is also category C.

♦ Allergy and Immunology

Persistent nasal congestion may accompany pregnancy (rhinitis of pregnancy).

OFFICE GYNECOLOGY

Office gynecology has been partially covered in previous sections. Especially review gynecologic infections in the Infectious Disease section, Book 1. Pap smear, ovarian cancer, and breast cancer are covered in the Oncology section, Book 4. Osteoporosis is discussed earlier in this section. Amenorrhea is discussed in the Endocrinology section, Book 4.

Postmenopausal Bleeding

A woman should undergo **endometrial assessment** if she has postmenopausal bleeding:

- In the absence of HRT therapy
- After she has been on combined HRT continuously for 1 year without bleeding
- At an unexpected time during cyclic replacement

Treatment Recommendations for Menopausal Symptoms

Vasomotor instability (hot flashes): short-term estrogen therapy (if no history of breast cancer or cardiovascular disease).

Urogenital atrophy: vaginal estrogen for moderate-to-severe symptoms; moisturizers and lubricants for mild symptoms.

Dysfunctional Uterine Bleeding (DUB)

DUB refers to excessive bleeding due to persistent anovulation in a reproductive-age woman with ovaries capable of producing estrogen. The patient's periods may be too frequent, too long, or with too heavy of a flow. DUB is a diagnosis of exclusion. There are **many** causes, including hypothyroidism, liver disease, renal disease, coagulopathies, pregnancy complications, anatomic lesions, and drugs, among others.

Treatment for **young** women with DUB is usually oral estrogen/progestin preparations. Oral contraceptives

Quick Quiz

- True or false? Dysfunctional uterine bleeding (DUB) usually does not require any workup.

containing 35–50 µg of ethinyl estradiol are often used. 4 tablets a day are given initially; this increases bleeding for 1–2 days and generally stops the bleeding in 3–4 days. The patient is then given 2 pills per day for 20 more days. Withdrawal bleeding will then occur within 2–5 days after ending treatment. This hormonal therapy is given for 2–3 more cycles, using 1 pill per day, and then stopped.

Premenstrual Tension Syndrome (PMS)

PMS is a group of symptoms, which most often start during the late luteal phase and are gone within 1–2 days of the onset of menses. The biochemistry of this dysfunction has not been established.

No single treatment has been proven effective, but the cause may be multifactorial, so there are many avenues of treatment to explore with each patient. You can achieve ovulatory suppression with oral contraceptives. These patients may also respond well to the newer mini pill, which contains only progestin. Other similar options include Depo-Provera® and Norplant®. Oral natural progesterone has been used with varying success.

Various dietary changes help some patients, such as avoiding caffeine, salt, sugar, alcohol, and/or chocolate. Vitamin supplements, such as vitamin B₆ and vitamin E, have also been effective for some. Magnesium 360 mg (as magnesium pyroglutamate carboxylic acid) orally tid, given from day 15 of menstrual cycle to the 1st day of menses, may also help. Note that no one of the above treatments is effective for everyone.

If pharmacotherapy is desired, use fluoxetine, sertraline, or paroxetine.

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I N T E R N A L M E D I C I N E R E V I E W



CORE CURRICULUM

15th EDITION

Robert A. Hannaman, MD
with Candace L. Walkley, MD

NEUROLOGY

NEUROLOGY

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COMA

OVERVIEW

Lethargy, confusion, stupor, obtundation, and coma are terms that apply to diminished levels of consciousness. Consciousness depends on the degree of a person's alertness and attention. **Both** the reticular activating system (RAS) **and** the cerebral cortex must be working effectively in order to sustain normal consciousness.

Thus, coma can be caused by **either** a decrease in the activity of the reticular activating system (RAS) **or** a process that involves the cerebral cortex of **both** hemispheres. The RAS resides within the brainstem, so injury to the brainstem, such as a hemorrhage in the pons or midbrain, can cause coma. Certain drugs (prescribed, OTC, and illicit) also affect the RAS directly.

Metabolic disorders are the most common cause of coma, with intoxications leading the list followed by anoxic brain damage.

Plum and Posner classify the causes of coma in the following ways:

- Supratentorial
- Diffuse
- Infratentorial
- Multifactorial
- Metabolic

WORKUP OF COMA

Neurologic Exam Findings

Overview

A thorough history and neurological exam are required to establish the diagnosis and the possible cause of coma. This includes a review of underlying medical and mental health illnesses, medications, ingestions, and intoxications. The Glasgow Coma Scale, though constructed originally to assess responsiveness of patients with cerebral trauma, is also used in the evaluation of other etiologies of acute coma. Components of the neurological examination must include observations about respiration (and respiratory patterns), pupils, and motor responses (or a lack thereof).

Also, vital signs including temperature, pulse, respiratory rate, and blood pressure can provide clues to the diagnosis.

Motor Responses

Motor responses, such as **decerebrate** and **decorticate** posturing, may help to localize the site of injury:

- Decerebrate posturing or rigidity occurs when the tonic labyrinthine reflex that resists gravitational force acts without modulation of the higher brain, causing **extension of all extremities**.
 - It indicates an effective **severing** of the brain from the spinal cord at the level of the **midbrain**,

specifically below the level of the red nucleus. This is often indicative of uncus (transtentorial) or tonsillar brain **herniation** (see below).

- It is seen in a variety of conditions such as midbrain compression by a mass, cerebellar or other posterior fossa lesions, and severe metabolic insults. It may also be seen in cerebral white matter disease and basal ganglia lesions.
- Decerebrate posturing is not seen much because it occurs in less common situations and is rapidly followed by death.
- Decorticate posturing (rigidity) is characterized by **flexion of upper limbs** with **extension of lower limbs**. It is caused by lesions at a more rostral level of injury to both corticospinal and rubrospinal tracts resulting from damage to brain areas which may include the cerebral white matter, internal capsule, and thalamus. These are **upper** motor neuron lesions. Causes may include traumatic brain injury, stroke, intracranial hemorrhage, brain tumors, and encephalopathy.

In uncus herniation, patients may progress from decorticate to decerebrate posturing.

Respirations

Cheyne-Stokes respiration describes a particular pattern of breathing in which the patient has periods of hyperventilation alternating with apnea. This pattern occurs in **bilateral** cerebral disease, **impending herniation**, and **brainstem** lesions; it can also be due to **metabolic** causes.

Apneustic breathing consists of rapid, deep breaths alternating with apneic pauses and is due to a lesion of the lower pons.

Ataxic breathing is very irregular and usually indicates a lesion of the medulla.

Central neurogenic hyperventilation. Lesions of the lower midbrain-upper pontine tegmentum cause central neurogenic hyperventilation, which produces an increase in the rate and depth of respiration resulting in advanced respiratory alkalosis.

Pupils

Remember that in the comatose patient, any **asymmetry** between the sizes of the pupils must be considered **pathologic** (Table 11-1). Light reactivity also needs to be carefully assessed.

Oculovestibular Testing

Oculocephalic (doll's eyes) and ice-water caloric testing (eyes look toward the cold) test the same vestibular-brainstem-ocular muscle pathway. The complete absence of eye movement in response to oculovestibular testing indicates either severe disruption of brainstem tegmental systems (**midbrain** or **pons**) or a profound overdose of sedative, anesthetic, or anticonvulsant drugs.

Table 11-1: Pupil Size in Coma

Size	Description	Cause	Examples
	One dilated unreactive pupil	Parasympathetic nerve problem	Oculomotor nerve compression from uncal herniation, rupture of an internal carotid artery aneurysm
	One pinpoint pupil (miosis)	Sympathetic nerve problem (Horner)	Lateral medullary syndrome, hypothalamus injury
	Two midsize nonreactive pupils	Parasympathetic and sympathetic nerve destruction	Midbrain disruption (can affect one or both pupils), anoxia, hypothermia, anticholinergics, severe barbiturate overdose
	Two dilated unreactive pupils		Anoxia, hypothermia, anticholinergics, severe barbiturate overdose
	Two pinpoint reactive pupils		Opiates, pontine destruction

Doll's eyes:

- Definition: When the head is turned, the eyes keep "looking" in the initial direction (eyes do not follow the movement of the head). Doll's eyes in a comatose person indicates that the brainstem is intact. **Absent** doll's eyes is a **poor** prognostic sign. Generally, doll's eyes are preserved in early metabolic coma. The exceptions are metabolic comas due to barbiturates and phenytoin.
- Testing for doll's eyes, which requires moving the head, should be done **only** after C-spine injury has been ruled out.

Reduction or absence of spontaneous **blinking** and loss of **corneal** reflexes are signs of deepening coma.

Scans and Lab Work for Coma

Quickly obtain a CT or MRI of the brain in order to narrow the differential, especially when the cause is unclear.

Check CBC, electrolytes, BUN, creatinine, glucose, ABG, urinalysis, and a toxicology screen for illicit drugs.

Other tests, such as an EEG, are helpful in identifying nonconvulsive status epilepticus, especially when there is a prior history of seizures. In one series of comatose patients in whom the cause was unknown, 8% were found by EEG to be in nonconvulsive status epilepticus.

Finally, you may need to do cerebrospinal fluid examination (including the usual bacterial and viral tests) if you suspect meningitis or encephalitis.

Evaluation of Findings

Supratentorial coma is due to an injury of the hemisphere(s).

There are 2 mechanisms:

1) Lateral (uncal) herniation: An expanding mass lesion (tumor, stroke, hemorrhage) forces the uncus under the tentorium. This puts pressure on the brainstem and, therefore, the RAS. Because of the course of the 3rd cranial nerve, the herniating uncus compresses this nerve, causing an enlarged pupil ipsilateral to the supratentorial lesion.

2) Central herniation: Injury to the thalamus (such as hemorrhage) results in diminished consciousness very early in its course. Later, the pupils are in mid-position and

become fixed. As the herniation continues, the course begins to merge with that of uncal herniation. In other words, central and uncal herniation syndromes can be differentiated early on, but, later, their courses merge.

Infratentorial coma is due to an injury that causes destruction or compression of the brainstem. Signs of infratentorial herniation include bilateral reactive pinpoint pupils (due to pontine involvement) and respiratory abnormalities, including cluster breathing, apneusis (deep gasping), and ataxic breathing. There are 3 possible causes:

- 1) Basilar artery occlusion with pontine infarction
- 2) Cerebellar infarction or hemorrhage
- 3) Posterior fossa neoplasms

Expansion of the contents of the posterior fossa forces the contents of this compartment in one of two directions: up (**upward herniation**) or down (**downward herniation**). Upward herniation pushes the posterior fossa contents up under the tentorium, compressing the brainstem. Downward herniation forces the cerebellar tonsils down through the foramen magnum, compressing the medulla.

Metabolic coma has many causes, including ischemia, hypoxia, hypoglycemia, organ disease (lung, liver, kidney), and drugs. Early in metabolic encephalopathy, patients have changes in respiratory pattern and mentation. The **pupils** are typically **reactive** until the terminal stages. Exceptions include anticholinergic toxicity, which causes fixed dilated pupils, and severe barbiturate intoxication. In addition, both hypothermia and anoxia/ischemia may cause fixed pupils of varying size. Anoxic-fixed pupillary dilatation lasting more than a few minutes implies severe and usually irreversible brain damage.

Quick Quiz

- What is the significance of doll's eyes?
- What pupil finding is associated with uncal herniation?
- Where is the presentation of locked-in syndrome?
- What is the definition of persistent vegetative state?

CONDITIONS THAT MIMIC COMA

LOCKED-IN SYNDROME

The locked-in syndrome is rare and most often caused by a lesion of the **ventral pons** as a result of **basilar artery occlusion**. The lesion typically spares the somatosensory pathways and the ascending RAS responsible for arousal and wakefulness, as well as midbrain structures that allow the eyelids to be raised. Thus the lesion interrupts the corticobulbar and corticospinal pathways, depriving the patient of speech and the capacity to respond except by vertical gaze and blinking. Persons with locked-in syndrome are awake and aware of the surrounding environment but may have only the ability to control eye movements. Typically, they can communicate only by using eye blinks and **vertical** eye movements (the efferent abducens nerve fibers controlling horizontal eye movements are usually destroyed). Because the cerebral cortex is spared, an **EEG** is **normal**. Some patients can recover some function, so treatment should be multidisciplinary and should include physical and speech therapy, pulmonary rehab, and help with swallowing.

VEGETATIVE STATE

Vegetative state results from severe **bilateral cerebral** dysfunction, often following a period of coma. Vegetative state is often caused by **anoxic brain damage** (e.g., after MI) and may be the terminal phase of progressive cortical degenerative processes such as **Alzheimer** and **Creutzfeldt-Jakob** disease.

These patients typically have normal sleep-wake cycles but no discernible cognitive function. Respiration may quicken in response to stimulation, and you may see certain automatisms such as swallowing, bruxism, grimacing, grunting, and moaning. There is loss of sphincter control. EEG abnormalities include low-amplitude delta-frequency background activity, burst suppression, widespread alpha and theta activity, an alpha coma pattern, and sleep spindles. Stimulating the patient causes minimal if any change in background EEG activity.

Neuropathology shows cortical laminar necrosis, which is often extensive, with a relative or complete sparing of brainstem structures (including the RAS).

Comatose patients who enter into vegetative states either recover or progress to death—usually within 2 weeks. Vegetative state that persists more than 3 months is called **persistent** vegetative state. Patients who do not recover after 3 months are unlikely to recover. Usually within 5 years, death occurs from pneumonia, urosepsis, or sudden death.

AKINETIC MUTISM

Patients with akinetic mutism are profoundly apathetic, although they register most of what is happening around them. They may speak normally and relate events from recent and distant past. This state is caused by **bilateral** lesions usually of the anterior parts of the **frontal lobes**, leaving intact the motor and sensory pathways.

CATATONIA

Catatonia is a state of stupor and of neurogenic motor immobility associated with psychiatric states such as schizophrenia, depression, PTSD, and drug abuse. Patients with catatonia are unresponsive although they preserve oculocephalic responses (doll's eyes). Some patients display a waxy flexibility of passive limb movement and hold seemingly uncomfortable limb postures for long periods (**cataplexy**). Peculiar motor mannerisms or repetitive motions, seen in a number of these patients, may give the impression of seizures. There are no signs of structural brain disease. The EEG is usually normal although it shows diffuse slowing with malignant catatonia.

BRAIN DEATH

The central features of brain death are an irreversible absence of all **cerebral** functions and absence of all **brainstem** functions, including spontaneous respiration. This usually results from catastrophic brain damage (e.g., trauma, cardiac arrest, cerebral hemorrhage), but you need to exclude reversible causes such as drug overdose.

Signs indicating the absence of **cerebral** function are the presence of deep coma along with the lack of spontaneous movement and motor and vocal responses to all visual, auditory, and cutaneous stimulation.

Indications of absence of **brainstem** function are:

- Loss of spontaneous eye movements
- Mid-position of the eyes
- Lack of oculocephalic (doll's eyes) and oculovestibular (caloric) responses
- Presence of dilated or mid-position fixed pupils (not smaller than 3 mm)
- Paralysis of bulbar musculature (no facial movement or gag, cough, corneal, or sucking reflexes)
- Absence of motor and autonomic responses to noxious stimuli
- Absence of respiratory movements

Absence of respiratory movements is confirmed by having the patient off the ventilator long enough for PaCO_2 to rise to $> 60 \text{ mmHg}$ following 10–20 minute ventilation with 100% oxygen.

Diagnosis of brain death requires documentation of loss of cerebral and brainstem functions listed above. EEG is helpful if it establishes that there is no activity in the cerebral cortex, but it is **not required** for diagnosis.

HEADACHE

OVERVIEW

The history and examination are crucial in diagnosing the type and etiology of headache, including the **quality** of pain (dull, sharp, throbbing, and constant), **location**, **duration**, **exacerbating** or **ameliorating** factors, and associated symptoms. Also important are the mode of onset of pain and variation over time. First, determine if the headache is primary or secondary.

The common **primary** headache syndromes are migraine, tension headache, cluster headache, or one of the trigeminal–sympathetic migraine variants of migraine or cluster. Primary headaches tend to be chronic, recurrent, and without signs of neurologic disease.

Secondary headaches are caused by an underlying condition:

- Cerebral aneurysm
- Intracerebral hemorrhage
- Subdural hematoma
- Increased intracerebral pressure (idiopathic intracranial hypertension, brain tumors)
- Strokes
- Trauma
- Sinus problems
- Temporal arteritis
- Acute angle glaucoma

MIGRAINE

Presentation

[Know.] Migraines are a common, largely familial disorder characterized by periodic, often unilateral, pulsatile (throbbing) headaches which begin in childhood, adolescence, or early adult life and diminish in frequency as patients get older. These headaches are typically unilateral (~ 60%) but not consistently on the same side (unlike vascular headache secondary to arteriovenous malformation). They last several hours (typical) to 3 days (rare). Triggers include emotional stress, certain foods (e.g., chocolate, **aged cheese**, and other foods that are rich in tyramine), alcohol (particularly red wine or port), menstruation, exposure to glare or other strong sensory stimuli (including perfumes), and rapid changes in barometric pressure. In women, they often occur in the premenstrual period and may be worsened by oral

contraceptives. Migraines are frequently associated with nausea, vomiting, sensitivity to smell, photophobia, and phonophobia. Movement of the head exacerbates the pain, while sleep and darkness may help lessen the pain.

Migraine with aura (previously called classic migraine) is **preceded** by an **aura**—most commonly visual symptoms, such as sparkling lights (scintillating scotomata) or jagged zigzag lines (fortification spectra) that move slowly across the visual fields for several minutes—and may leave scotomatous defects.

Migraine without aura (previously called common migraine), occurs without an aura and is 5 times more common than migraine with aura.

Complicated migraine (rare) is associated with **focal** neurologic symptoms, including numbness and tingling of the lips, face, and hand (on one or both sides), arm or leg weakness, slight confusion, and/or dizziness. In any given patient, only a few of these phenomena are present, and they tend to be stereotyped with each attack. If symptoms spread from one part of the body to another or evolve over time, they do so relatively slowly, over several minutes (not seconds, as in seizures). Such symptoms last 5–15 minutes on average and are followed by unilateral headache. The neurologic deficits can be prolonged but are rarely permanent.

Basilar migraine affects the **brainstem**. Patients are usually young women or children with a family history of migraine. They may develop:

- visual phenomena that occupy **both** visual fields (temporary cortical blindness may occur),
- vertigo,
- dysarthria,
- staggering,
- **incoordination** of the limbs,
- diplopia (“seeing double”), and
- tingling.

Tingling may occur in both hands and feet and sometimes around both sides of the mouth.

These symptoms last 10–30 minutes and are usually followed by an occipital headache. In exceptional cases, coma or transient quadriplegia may develop.

Acephalic migraine (migraine without headache) may present with abnormal transient neurologic dysfunction such as visual symptoms, focal sensory deficits, transient aphasia, or hemiparesis. This type frequently occurs with advancing age in patients who previously experienced migraines with or without aura.

Status migrainosus is characterized by multiple or virtually continuous headaches with persistent scalp tenderness, over 72 hours or longer.

Quick Quiz

- How is brain death diagnosed? Is an EEG required?
- Name some triggers of migraine headaches.
- What is the main difference between a complicated migraine and a migraine with aura?
- Which migraine patients should not receive a triptan drug?

Acute Treatment of Migraine

Acute treatment refers to any treatment that is given within the **1st hour** of the headache. Acetaminophen, aspirin, and NSAIDs are effective in some patients, especially if the migraine is mild and infrequent. Next is the “**triptans**”:

- Sumatriptan (Imitrex®)
- Zolmitriptan (Zomig®)
- Rizatriptan (Maxalt®)
- Naratriptan (Amerge®)
- Almotriptan (Axert®)
- Eletriptan (Relpax®)
- Frovatriptan (Frova®)

No head-to-head trials yet exist comparing the triptans; therefore, which to choose is based on a few features of the drugs:

- Rizatriptan works fastest. But know that concomitant use of propranolol requires that you adjust the rizatriptan dose downward (propranolol increases the levels).
- Sumatriptan has 3 methods of delivery (injection, intranasal, and oral).
- Combination tablet of sumatriptan + naproxen works better than taking either agent alone (and better than taking either agent as a separate pill, at the same time).

Because of risk of inducing ischemia, do **not** use triptans for any of the following conditions:

- Complicated or basilar migraines
- Coronary heart disease (CHD) or Prinzmetal angina
- History of stroke
- Uncontrolled blood pressure
- Pregnancy

Also, do not combine triptans with monoamine oxidase inhibitors or use within 24 hours of ergot drugs.

Instead of the triptans, IV **prochlorperazine** or **metoclopramide** also is effective for termination of migraine in patients who present to the Emergency Department with vomiting. Diphenhydramine, 25 mg IV, helps prevent the unusual dystonic reaction.

Dihydroergotamine (DHE) may be effective in some patients, but it also must be avoided in patients with CHD, HTN, history of peripheral vascular disease, and liver or kidney disease. You may try narcotics, but their use should be restricted to 2 days per week. Oral or IV corticosteroids can be used to terminate status migrainosus.

Increased use of any medication, including triptans and NSAIDs, to treat frequent headaches can incite a **rebound** called “medication overuse headaches.” Patients should be instructed not to take analgesics more than 10 days per month. If they need meds this often, then prescribe prophylactic treatment.

Prophylactic Treatment of Migraine

Migraine seems to be associated with an increased risk of ischemic stroke, especially in certain groups of women who have recurrent headaches with aura. The American Stroke Association 2010 guideline on primary prevention of stroke recommends **prophylaxis** for women with frequent migraines with aura, if younger than **55 years**, and especially if they are taking **oral contraceptives**.

For other patients, the **frequency** of headache determines whether prophylaxis is needed: Usually, the threshold is > 2–3 headaches per month. There is usually a lag of 2–4 weeks between the start of prophylaxis and its effect.

The major categories of migraine prophylaxis agents are:

- **β-blockers.** Propranolol and timolol are FDA-approved for migraine, but atenolol, metoprolol, and nadolol are also used; **not** recommended in patients older than **60 years** and/or **smokers**.
- **Tricyclic antidepressants.** Amitriptyline; side effects = oversedation, dry mouth, palpitations, orthostasis, blurry vision, weight gain, constipation, and short-term memory impairment or confusion—especially in the elderly, or those with baseline cognitive impairment.
- **Tetracyclic antidepressants.** These are serotonin receptor blockers (mirtazapine, venlafaxine) also known as noradrenergic and specific serotonergic antidepressants (NaSSA).
- **Anticonvulsants** (valproate, topiramate), which are sometimes used off-label.
- **Calcium channel blockers** (verapamil, nimodipine) may develop tolerance.
- **ACE inhibitors and ARBs** (lisinopril and candesartan).
- **NSAIDs.**
- **SSRIs.** There is not enough data for SSRIs; they may even cause headaches.

Definitely use prophylactic agents to treat complicated and basilar migraines. Relaxation techniques also may be helpful for patients to prevent headaches.

CLUSTER HEADACHE

Cluster headache is a distinct syndrome that frequently responds to treatment with oxygen. The term “cluster” is derived from the periodicity of the headaches: They can occur up to several times/day for a few weeks before remitting. Cluster headache becomes chronic in 10% of patients. Occasionally this headache is referred to as the “suicide headache,” because the associated pain is so intense that some patients have committed suicide when they were unable to get relief from a cluster episode.

The daily attacks may occur at the same hour each day (in 50% of patients). The pain is **unilateral**, severe (described as an “ice-pick” or “hot poker”), and **peri- or retro-orbital**. It peaks quickly in 5–10 minutes and resolves in an hour or two.

Another characteristic feature is nightly recurrence, about 1 to 2 hours after the onset of sleep or several times during the night. The cluster headache has been called the “alarm clock headache” because it recurs regularly each night for 6 to 12 weeks, followed thereafter by complete freedom for many months or even years.

Associated vasomotor phenomena include ipsilateral blocked nostril, rhinorrhea, lacrimation, miosis, and flush and edema of the cheek that last about 45 minutes.

Cluster patients tend to be restless during attacks, as opposed to most migraine sufferers who prefer a dark, quiet room and stillness. **70%** of patients find that **alcohol** triggers their headache. Adult men, age range 20–50 years, are affected much more often than women (5:1).

Treatment: The best acute treatment is **oxygen**. Inhalation of oxygen at 6 L/min x 15 minutes is usually **rapidly abortive**, acting to inhibit neuronal activation in the trigeminocervical complex. However, this is not always practical or available. Subcutaneous and intranasal triptans are effective and can be combined with oxygen; but remember, the triptans should not be used in patients with a history of or strong risk factors for CHD and stroke. For patients who don’t get better with O₂ and can’t take triptans, octreotide and intranasal lidocaine are options.

Once a patient experiences the first of what will become a cluster episode, **prophylactic** treatment can be instituted. Verapamil is the drug of choice (outpatient oral titration up to 480 mg), but monitor the patient’s pulse and ECG for bradycardia and heart block when titrating higher than 240 mg. Other drugs sometimes used include lithium, methysergide, prednisone, and topiramate. The corticosteroids are used as acute drugs while waiting for verapamil to work. Taper off the meds once the cluster is over.

TENSION HEADACHE

Tension headache, the most common variety of headache, is characterized by pain that is chronic, bilateral, constant, non-throbbing, “squeezing,” and devoid of migrainous or cluster features. It may be intermittent or

chronic. Unlike most other headaches, it can be present throughout the day for long periods of time. Sleep is usually undisturbed, but headache returns upon awakening. It is more common in women. A third of patients with chronic tension headaches have symptoms of depression.

Treatment: Aspirin, acetaminophen, or NSAIDs can be used for acute attacks.

Preventive medication should be considered when attacks occur more than 2 days per week—this should help prevent medication overuse, which may predispose to chronic headache. Limiting treatment to 9 days per month (2 doses of meds/day) helps prevent this complication. Effective prophylactic drugs include amitriptyline and other tricyclics, tetracyclics (serotonin receptor blockers [mirtazapine, venlafaxine—see migraine prophylaxis above]), and gabapentin. Not SSRIs. Relaxation, biofeedback, and behavioral therapy are helpful in dealing with the tension that brings about the headaches.

BENIGN SEXUAL HEADACHE

Also called “coital headache,” benign sexual headache occurs more often in men than women (4:1). The headache occurs either as a tension type headache as sexual excitement increases or as a severe, throbbing headache at the time of orgasm. These headaches can persist for several minutes or hours; they are **benign**.

If the headache does not resolve after **2** hours or is accompanied by neck stiffness, vomiting, and/or neuro deficits, rule out an underlying AV malformation with or without subarachnoid hemorrhage. Evaluate with urgent neuroimaging.

POST-TRAUMATIC HEADACHE

Post-traumatic or post-concussion headache may occur even after a minor head injury. It may be vascular, like migraine; however, some have proposed that the headache is due to abnormal neurotransmission within the brain. Accompanying symptoms include dizziness, fatigue, insomnia, nervousness, irritability, and inability to concentrate. Symptomatic treatment is usually effective, and the headache often spontaneously remits. Patient reassurance is important.

GIANT CELL ARTERITIS

Giant cell (temporal) arteritis usually occurs in patients > 55 years old. History is usually a recent onset of headache. Jaw claudication, fatigue, weight loss, and low-grade fever may be associated symptoms. Up to 50% of patients have a history of polymyalgia rheumatica. Do not miss this diagnosis! If untreated, ischemic optic neuropathy can cause irreversible vision loss.

Physical exam may show temporal artery tenderness. The erythrocyte sedimentation rate usually is very

Quick Quiz

- What are the clinical features of cluster headache?
- How do you treat cluster headache?
- Name some risk factors that are associated with IIH.
- What is the clinical presentation of IIH?
- What is the current definition of “dementia”?

elevated, but C-reactive protein is a more sensitive marker of inflammation. Do a **temporal artery biopsy** if the diagnosis is suspected. More in the Rheumatology section, Book 3.

IDIOPATHIC INTRACRANIAL HYPERTENSION / PSEUDOTUMOR CEREBRI

Idiopathic intracranial hypertension (IIH; also called pseudotumor cerebri) is a set of signs and symptoms—headaches, papilledema, and loss of vision—caused by **increased intracranial pressure**. It usually occurs in obese, premenopausal, women (90%) and may occur during pregnancy. It rarely occurs in children or in men.

Obesity is strongly correlated (90–95% of patients) and causal; with the increasing obesity of the U.S. population, the incidence of IIH is also increasing.

Drugs that are associated with IIH include vitamin A (especially in the form of isotretinoin, used for the treatment of severe acne), tetracycline, and corticosteroids; but the condition may also be precipitated by steroid withdrawal.

Severe, irreversible vision loss is the major morbidity. It occurs in > 6% of patients and is twice as common in men as in women.

The cardinal symptom of IIH is a **morning** headache described as dull or as a feeling of pressure, made worse by **coughing** or straining. There is almost always (70–100%) a **peripheral visual field loss** accompanied by blind spots that may be noticeable only with formal visual field testing. **Pulse-synchronous** tinnitus may be present.

Other, less-frequent complaints are blurred vision, dizziness, minimal horizontal diplopia from 6th nerve paresis, transient visual obscurations that often coincide with the peak intensity of the headache, or mild numbness of the face on one side.

On exam, **papilledema** is a hallmark finding. 6th nerve palsy may be obvious either unilaterally or bilaterally. CT/MRI is typically **normal**, with absence of deformity, displacement, or obstruction of the ventricular system—but may show “slit-like” ventricles. The CSF pressure

is elevated, usually in the range of 250–450 mm H₂O. (Normal CSF pressure is generally < 200 mm H₂O.)

Treatment of IIH includes a low-sodium weight-reducing diet, symptomatic treatment for headaches, and prevention of vision loss. **Repeat lumbar punctures** with drainage of sufficient fluid to maintain CSF pressure less than 200 mm H₂O helps ~ 25%, but drugs usually are given and include:

- Carbonic anhydrase inhibitors (acetazolamide) with loop diuretics
- Loop diuretics alone
- Prednisone

Prednisone works acutely but is **not** recommended for chronic cases of IIH because of side effects, not the least of which is increasing intracranial pressure. Unilateral optic nerve sheath fenestration may preserve vision in the acute setting.

In patients whose headaches are unresponsive to medications and weight reduction, lumbar-peritoneal shunt may have considerable success.

THALAMIC PAIN SYNDROME

This syndrome causes refractory unilateral pain, which may affect the trunk, as well as the arm and leg. Thalamic pain syndrome may follow weeks to **years** after a thalamic infarct (with hemisensory loss).

DEMENTIA

DEFINITION

Dementia is defined as **cognitive or behavioral** impairments that:

- Are **progressive**
- **Interfere** with normal daily functioning
- Are **not** due to **delirium** or an underlying **psychiatric disorder**

Note how this definition contrasts with encephalopathy, which causes altered states of consciousness—from delirium to stupor. This topic is also discussed in the General Internal Medicine section, Book 5, under Geriatrics.

WORKUP

Evaluating Domains of Function

According to multiple guidelines by the Institute of Aging and the Alzheimer’s Association, dementia is diagnosed **only** after completion of the following 3 tasks, which evaluate specific “domains” of function (discussed next):

- 1) The health care provider performs a thorough **H&P** that includes obtaining history from the patient **and** an additional informant (because history from a potentially demented patient is not always reliable).

- 2) **Neuropsychiatric** testing (to exclude underlying psychiatric diagnoses).
- 3) Objective **cognitive** assessment using a validated tool (e.g., the Mini-Mental State Exam).

Diagnosis of Dementia

Dementia is diagnosed when abnormalities exist in **2 or more** of the following **domains**, and when the abnormalities also are **progressive** and **interfere** with daily functioning:

- **Memory** = Acquiring and/or remembering new information: Do they ask repetitive questions, lose items, or get lost?
- **Executive function** = Reasoning and performing complex tasks: Do they understand appropriate danger? Can they perform their ADLs, such as grocery shopping?
- **Perception** = Assessing visuospatial orientation: Do they recognize faces and objects? Can they dress themselves?
- **Words** = Speaking appropriate language: Do they have problems recalling common words without hesitations?
- **Behavior** = Behaving normally and appropriately: Is there undue agitation, apathy, loss of empathy, compulsive behavior?

Psychosis that is refractory to treatment is a common feature of advanced dementia.

Minor Cognitive Impairment

When only **1 of the domains** is in decline, but the impairment does **not** significantly impact daily functioning, the diagnosis is “minor cognitive impairment” (**MCI**).

MCI can be either amnesic or non-amnesic. Amnesic MCI is most common. Not all patients with MCI deteriorate into dementia. Patients with amnesic MCI have memory impairment that does not significantly impact daily living, and general cognition is intact. Of those who do deteriorate to Alzheimer disease, more often they are the patients with amnesic MCI.

Patients with non-amnesic MCI have impairment in one of the other domains (executive function, perception, words, or behavior), but daily living is not impacted. General cognition is intact.

Reversible Causes

In evaluating dementia, exclude the following treatable causes of impaired cognition:

- Medications
- Vitamin B₁₂ deficiency (may have associated polyneuropathy/myelopathy)
- Heavy metal poisoning (arsenic, mercury, and lead)
- Hypothyroidism

- Chronic subdural hematomas (consider especially in alcoholics, in patients on anticoagulants, and in elderly patients with a history of falls)
- Normal pressure hydrocephalus
- Tumors, especially involving the frontal lobes
- Infection and inflammation:
 - AIDS
 - Neurosyphilis
 - Neurosarcoidosis
 - Chronic meningitis
 - Lupus cerebritis
 - Vasculitis

CAUSES OF DEMENTIA

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is a potentially **treatable** cause of dementia. It is characterized radiologically by enlargement of the ventricles without obstruction of the aqueduct (i.e., a “**communicating hydrocephalus**”) and **no** cortical atrophy, which is associated with hydrocephalus “ex vacuo.”

NPH often occurs after head **trauma**, **meningitis**, or **subarachnoid hemorrhage**—and a history of one of these premorbid conditions appears to be the best predictor of a beneficial response to shunting (see below). One thought about how this develops is that there is obstruction of the outflow of cerebrospinal fluid at the level of the arachnoid granulations. However, the intracranial pressure is **normal**, there is **no** papilledema, and the person has **no** headache.

NPH causes the **classic triad** of:

- 1) a gradually worsening **dementia**,
- 2) gait ataxia/apraxia (a “**magnetic**” gait, with the feet apparently glued to the floor), and
- 3) **urinary incontinence**.

Often, the gait problems and incontinence precede the dementia. Patients may present with frequent falls due to gait instability.

Differentiate NPH from ventricular dilatation caused by diffuse white matter changes (Binswanger disease, see below) which is more common in patients with hypertension or diabetes mellitus. Note that it may present with the **same clinical triad** as NPH.

Treatment. In most cases of NPH, the CSF opening pressure is above 155 mm H₂O, and the cell count is normal. The treatment is **ventriculoperitoneal** or **ventriculoatrial shunt**. Certain tests may help to identify patients who are most likely to respond to shunting. These include clinical response to lumbar puncture (LP), isotope cisternography, and dynamic MRI, which measures the direction of CSF flow (but none of these tests is universally reliable). The most consistent improvement is attained in patients with an identified cause such as subarachnoid hemorrhage, chronic meningitis, or tumor of the 3rd ventricle.

Quick Quiz

- Which 5 domains may be impaired in patients with dementia?
- What is the definition of minor cognitive impairment?
- What is the clinical triad in normal pressure hydrocephalus?
- How is AD diagnosed?
- How are CSF tau measurements used in the diagnosis of AD?
- What drug is used with a CI for the treatment of advanced AD?

Alzheimer Disease

AD Diagnosis

Alzheimer disease (AD) is the most common cause of dementia **after age 60**. 1st degree relatives have a 4x normal increased risk of developing it.

According to 2011 guidelines, AD is diagnosed when the illness is **insidious**, **progressive**, and marked by impairments in **2 or more** domains (memory, executive functioning, perception, words, and behavior) such that there is **significant impairment** in normal daily functioning. As with MCI (page 11-8), the amnesic presentation of AD is the most common. Patients with Alzheimer's have a **normal LP**.

Initial signs of AD usually reflect hippocampal dysfunction, with poor immediate recall and short-term memory. Impairment of naming may also be an early sign. As the disease progresses, impairments emerge in visuospatial and executive domains, reflecting dysfunction in the **parietal** and **frontal** lobes, respectively. Changes in environment (such as vacations or hospital stays) may be disorienting, and the patient may become lost on walks or while driving.

Note the contrast in the presentation of AD with the presentation of Lewy body and frontotemporal dementias, and sporadic Creutzfeldt-Jakob disease, which are seen in younger patients and have a **more rapid** and **volatile** course (more in the next section).

Also in contrast, multi-infarct dementia presents with **stepwise deterioration** that is often accompanied by motor or sensory impairment related to the areas of stroke.

Do **not** use any of the following for diagnosis of AD: MRI scans that show disproportionate atrophy, PET scans demonstrating amyloid deposition or decreased tracer uptake, and CSF tau measurements. These biomarkers are **not specific enough** yet, and abnormalities sometimes are seen in patients with normal cognition or MCI only.

Additionally, do **not** diagnose AD as a cause of dementia if the patient:

- has a history of significant cerebrovascular disease,
- has clinical features of Lewy body or frontotemporal dementia,
- has evidence of another psychiatric or neurologic illness, or
- takes a medication that can cause cognitive impairment.

These must be ruled out as causes of the dementia symptoms.

In an elderly patient presenting with dementia without a movement disorder, the main diagnoses to consider are Alzheimer disease, **vascular** dementia, and **mixed** dementia (with both neurodegenerative and vascular components).

AD Treatment

First-line treatment for Alzheimer's is the cholinesterase inhibitors (**CI**s):

- Donepezil (Aricept®)
- Rivastigmine (Exelon®)
- Galantamine (Razadyne®)

Note: Tacrine (Cognex®) causes liver toxicity and is no longer used.

Additive drug treatment includes the N-methyl-D-aspartate receptor antagonist memantine (Namenda®).

The **combination** of CI + memantine appears to be better than CI alone, especially for advanced AD.

The CIs produce a small improvement in cognition and, sometimes, in neuropsychiatric instability. Data are conflicting on their long-term effects. Not every patient receives benefit. Note that these drugs are for dementia only and should **not** be used to treat minor cognitive impairment (MCI). Best results with CIs are achieved in mild to moderate Alzheimer disease, but other types of dementia (e.g., multi-infarct and Lewy body dementia) sometimes also improve.

Dose escalations for each of these medications must be carried out over 4–6 weeks to minimize side effects. The main side effects are anorexia, nausea, and occasionally diarrhea or bradycardia (cholinergic symptoms). Rivastigmine is available as a patch that has fewer GI side effects and is useful in demented patients who will not swallow medications.

The neuropsychiatric instability of late-stage AD is common and difficult to treat. Mild to moderate depression in the early stages may respond to SSRIs, trazodone, or CIs, but definitely avoid tricyclic antidepressants because of the anticholinergic constipation and

urinary retention. Atypical antipsychotics (olanzapine, quetiapine, risperidone, clozapine) have been used to treat the agitation, insomnia, delusions, aggression, and wandering, but in 2011, the FDA published an advisory that these drugs are associated with **increased mortality** in the elderly with dementia (any cause). They should be used only in the most extreme cases of psychosis.

Vascular Dementia

Overview

Dementia associated with cerebrovascular disease can be divided into two general categories: **multi-infarct** dementia and **diffuse white matter** disease (Binswanger disease).

Multi-infarct Dementia

Multi-infarct dementia is the term used for the chronic cognitive deficits that can occur in patients who have had several strokes. The strokes may be large or small but usually involve several different brain regions. The occurrence of dementia depends partly on the total volume of damaged cortex, but is also more common with left hemisphere lesions. Multi-infarct dementias usually have prominent motor, reflex, visual, and gait abnormalities, but they typically do **not** involve difficulty in **naming** of objects, as associated with Alzheimer disease. Another difference is the clinical course of symptoms. Multi-infarct dementia has an **abrupt** onset with **stepwise** deterioration of mental function, with more prominent fluctuations of cognition. By contrast, **Alzheimer's** has a **slow**, steady progression.

Diffuse White Matter Disease

Chronic hypertension is the most common cause of dementia due to lacunar infarcts and diffuse white matter changes that are visible on MRI. The changes result from chronic ischemia mediated by occlusive disease of small, penetrating cerebral arteries and arterioles.

Early symptoms include mild confusion and impairments in memory, perception, and executive functions. Marked difficulties in judgment and orientation develop later, along with dependence on others for activities of daily living. Neuropsychiatric symptoms (apathy, anxiety, psychosis, euphoria, depression, aggression) also develop as the infarcts accumulate. Pyramidal and cerebellar signs may be seen. With advanced disease, urinary incontinence and dysarthria with or without other pseudobulbar features (e.g., dysphagia, emotional lability) are frequent.

Frontotemporal Dementia

Frontotemporal dementia (FTD; previously Pick disease) is quite similar in presentation and course to Alzheimer disease, but it is characterized by a **more rapid** and significant change in personality and behavior,

often with **disinhibition**, **language deficits**, or both. The onset is in the 5th to 6th decades (relatively young, compared to Alzheimer's), and the incidence in males exceeds females.

Common behavioral features include apathy, disinhibition, weight gain, food fetishes, compulsions, and emotional distance or loss of empathy.

Cognitive testing typically reveals spared memory but impaired planning, judgment, or language. Patients often show an absence of insight into their condition.

The naming of FTD subtypes is evolving based on their primary manifestations; e.g., behavioral variant vs. progressive nonfluent vs. semantic. Patients with FTD have more focal atrophy of the frontal and temporal lobes on CT or MRI scan, compared with the diffuse atrophy of Alzheimer's. However, histology is the only sure way to differentiate between the two, usually at autopsy.

Currently, there are **no** primary pharmacologic treatments for the frontotemporal dementias. Trazodone has been shown to result in some behavioral improvement, mainly in irritability, agitation, depressive symptoms, and eating disturbances.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is one of the very rare (1 per million people) **prior** diseases. It's mainly an infectious illness.

Based on observations of causes, CJD is divided into **sporadic** (sCJD, most common, 95%), **familial** (about 5%), **iatrogenic** (iCJD), and **variant** (vCJD). Usually, sCJD presents around ages 55–65, and we have no idea what causes it. When you see CJD in younger patients, think either iCJD or vCJD. vCJD is believed (but not definitively proven) to be caused by the prion that causes "**mad cow disease**" (bovine spongiform encephalopathy) in cattle. It appears that the prion jumped species and now infects humans. iCJD is caused by receipt of infected human tissues, hormones (growth hormone, gonadotropins, dural grafts, corneal or liver transplants), or exposure to contaminated surgical instruments. Familial CJD has genetic associations.

Regardless of cause, CJD develops as a **rapidly progressive** dementia (weeks as opposed to years) with characteristic **startle myoclonus** (response to loud noises or startle). The early stages of the neurologic disease are characterized by changes in behavior, emotional response, and intellectual function, often followed by ataxia and visual distortions, confusion, hallucinations, delusions, and agitation. Dementia and muteness quickly follow the early symptoms. Younger patients with vCJD tend to have dementia with predominantly **psychotic** features. The disease involves the cerebral cortex, basal ganglia, and spinal cord.

Quick Quiz

- What is a potential complication from the use of atypical antipsychotics in elderly patients with dementia?
- Compare and contrast the features of normal pressure hydrocephalus, Alzheimer disease, and vascular dementia.
- How does the clinical presentation of frontotemporal dementia differ from that of Alzheimer disease?
- How do you diagnose Creutzfeldt-Jakob disease?
- What is the problem with using antipsychotic drugs to treat patients with Parkinson dementia?

The diagnostic gold standard is brain **biopsy**. Supportive studies include:

- T1/T2 **MRI** with diffusion weighted images and FLAIR sequences (helps also to differentiate sCJD from vCJD)
- **EEG** (characteristic pattern of “periodic sharp waves complexes” on a diffusely slowed background)
- **14-3-3 protein** in an otherwise bland CSF (Only the National Prion Disease Pathological Surveillance Lab does this test, at Case Western, and sensitivity/specificity is < 80%.)

Creutzfeldt-Jakob disease is **fatal** in less than 1 year in > 90%.

Parkinson Disease Dementia (PDD)

Parkinson disease (PD) is caused by a loss of dopaminergic neurons in the substantia nigra. (See the later discussion under Movement Disorders on [page 11-40](#).)

Dementia in PD (PDD) is common, affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to Alzheimer disease, primarily affects **executive functions** and **attention**, with relative sparing

of language, memory, and calculations. When dementia precedes, or develops within 1 year after, the onset of motor dysfunction, it is referred to as **dementia with Lewy bodies (DLB)**. Neuropathology shows Lewy bodies mixed with amyloid plaques and neurofibrillary tangles characteristic of Alzheimer disease ([Image 11-1](#)). Lewy bodies are spherical eosinophilic inclusions within the neuron ([Image 11-2](#)).

The Lewy body elements seem to correlate most with the degree of dementia, so Parkinson disease dementia is frequently called DLB. DLB sometimes occurs **without** preceding Parkinson disease—but is otherwise the identical disease.

The core clinical features of PDD/DLB (besides dementia) are spontaneous motor features of parkinsonism; recurrent, vivid, visual hallucinations (usually paranoid persecutions); and prominent fluctuations of attention and cognition.

Both the dementia and psychosis may be at least partially responsive to acetylcholinesterase inhibitors and memantine. For unknown reasons, patients with DLB have dramatic and poor responses to antipsychotic drugs, including haloperidol and even the newer neuroleptics, clozapine and quetiapine. As mentioned in the section on Alzheimer’s, these drugs are under an **FDA safety advisory** because they are associated with an **increased risk of death** when used in elderly patients with dementia, and especially so in those with DLB. These drugs should be used with extreme caution and only in the smallest doses.

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) has its onset typically in the 6th decade, with clinical features such as difficulty in balance, abrupt falls, visual and ocular disturbances, slurred speech, dysphagia, and sometimes vague changes in personality. Difficulty in voluntary vertical movement of the eyes, often downward but sometimes only upward, and later impairment of voluntary saccades in all directions are characteristic. Cognitive slowing and dementia are prominent features.

Buzzwords for PSP: dementia with gaze palsy and falls.

Huntington Disease

Huntington disease (HD) causes both a **dementia** and a **movement disorder**. (See Other Movement Disorders starting on [page 11-43](#).) The gene responsible for HD is the **HTT** gene on chromosome 4p which codes for a mutant huntingtin protein that is probably toxic. (Note: The protein is spelled with an “i”, while the disease is spelled with an “o”.) It is inherited in an autosomal dominant fashion with complete penetrance. Problems typically begin in persons in their **late 30s**.

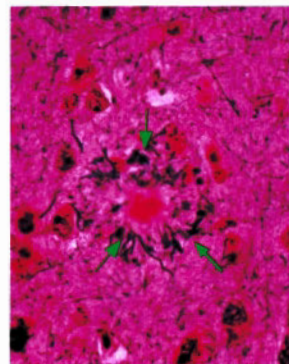


Image 11-1: Senile plaques with amyloid core

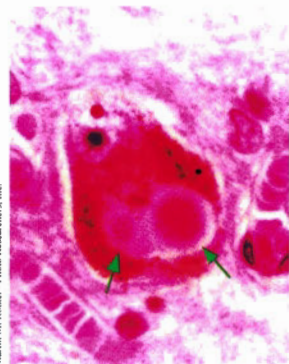


Image 11-2: Parkinson disease with Lewy bodies

HD causes dementia, **chorea**, and psychiatric disturbances, including personality changes, depression, and **psychosis**. Memory is relatively spared. Chorea is usually the heralding symptom. The emotional disturbances and changes in personality may be so severe as to cause psychosis with persecutory delusions or hallucinations.

Disease is progressive with death (typically from pneumonia) within 30 years after symptoms begin.

Diagnosis is made in the setting of positive family history, clinical features, and genetic testing demonstrating the *HTT* gene.

Atrophy of the caudate nuclei on CT or MRI ("boxcar" ventricles) is characteristic and correlates with deterioration in cognition.

No curative medication exists, and the disease is invariably **fatal**. Tetrabenazine has been approved and is effective in controlling mild **chorea**. Side effects are significant and include depression, sedation, and bradykinesia. Other symptoms can be ameliorated with antipsychotics (neuroleptics), benzodiazepines (e.g., clonazepam), and antidepressants.

Genetic counseling is available for family members but is performed only ~ 15% of the time. There are no guidelines that specifically recommend screening because of the gravity of the diagnosis, if the test is positive.

AIDS

AIDS is the most common cause of dementia in younger patients. Dementia affects half of all AIDS patients not on antiretroviral therapy (ART). The manifestations can be mild (minor cognitive-motor disorder) to severe (HIV-associated dementia). Impairment is related to the degree and duration of immunosuppression. Controlling the virus in a patient who has had AIDS for a prolonged period, with a low CD4 count, often does not reverse dementia.

HIV/AIDS dementia is associated with cognitive impairment, movement disorders, and depression. It starts with small comprehension problems and anhedonia, accompanied by tremor and gait abnormalities. Over time, patients develop slower movements with substantial cognitive impairment. Exclude opportunistic infections of the CNS as part of the workup.

Treatment includes treating the HIV with ART, focusing specifically on designing a regimen of medications that enter the CNS at higher levels (although this has not been shown to cause neurologic improvement). Associated depression should also be treated. More on treatment of AIDS in the Infectious Disease section, Book 1.

More on HIV-associated dementia on [page 11-18](#).

Depression

Some patients with **major depression** present with significant cognitive dysfunction, known as depressive

"pseudo-dementia." One differentiating feature is that **frontal lobe** release signs (e.g., grasp, suck, rooting, and palmomental reflexes) are common in patients with dementia, particularly if moderate or advanced, but they are **not** seen in isolated depression. In addition, immediate recall is usually poor in depression, due to attentional dysfunction, but good in dementia.

Depression can be reactive or endogenous. Symptoms are the same for both. In endogenous depression, patients, as expected, may have an abnormal response to the dexamethasone suppression test in which the cortisol is initially suppressed, but the duration of suppression is shortened (normal is > 24 hours).

DIZZINESS

SIGNS AND SYMPTOMS

When the term "dizziness" is used, one should try to differentiate among the following:

- Vertigo = a sense of spinning or swaying.
- Lightheadedness = presyncope ("I feel like I'm going to pass out").
- Imbalance = unsteadiness.
- Vague = not one of the 3 above. It may be hard for the affected person to describe.

Nystagmus is an involuntary oscillation of the eyes. The movements may be **pendular** (like a pendulum) or **jerk**. Jerk nystagmus has 2 components: slow and fast. The eyes "drift" (= slow component), and try to quickly recover (= fast component). The type of nystagmus may indicate its cause. For instance, drugs (e.g., antiepileptic medications) may cause **horizontal and vertical gaze-evoked** nystagmus (occurring when the person looks right, left, or up)—in other words, it is present "in all directions." Isolated vertical gaze-evoked nystagmus usually indicates disease in the posterior fossa.

Jerk nystagmus is most common in **vestibular** disorders, but does not indicate whether the lesion is within the central nervous system, or if it involves the cranial nerve itself. **Upbeating** jerk nystagmus usually indicates a lesion in the pons but can be seen in lesions of the medulla or cerebellum. **Downbeating** jerk nystagmus indicates a lesion at the cervicomedullary junction.

CAUSES OF VERTIGO

Benign Positional Vertigo

Benign positional vertigo (BPV) describes recurrent, brief episodes of vertigo that are brought on by the motion of changing head position.

It is thought to be due to loose otoconia in the semi-circular canal. Otoconia are crystals that reside in the saccule and utricle. When they escape this region, they may set up eddy currents in the endolymph causing

Quick Quiz

- What are the clinical features of Huntington disease?
- Name some features that distinguish depression from dementia.
- Name the maneuvers frequently employed to treat BPV.
- What are the clinical features of Ménière disease?
- Which TIAs cause vertigo?

symptoms of vertigo. BPV may also be caused by head trauma, labyrinthitis, or aging.

Most BPV resolves spontaneously over a couple of weeks or can be treated successfully with various repositioning maneuvers that move the otoconia to a position of the inner ear that is less likely to induce vertigo. These are the **Epley** and **Semont** maneuvers and their variations. In some patients, episodes recur periodically from several days to many months—rarely for years.

Meclizine doesn't cure BPV, but it is sometimes used to control nausea. BPV (and other causes of vertigo) is discussed thoroughly in the General Internal Medicine section, Book 5.

Vestibular Neuritis

Vestibular neuritis (vestibular neuronitis, acute peripheral vestibulopathy) causes a sudden onset of **non-positional** vertigo that is **self-limited** but may last weeks to months and occasionally can recur. This disorder occurs mainly in young to middle-aged adults, without preference for either sex.

Vestibular neuritis is caused by an inflammatory process affecting the vestibular portion of the **8th** cranial nerve and can be associated with viral infections. Pure vestibular neuritis does not affect hearing. If hearing is affected, it means it is no longer solely the nerve being affected but also the labyrinthine canals—and this is called vestibular **labyrinthitis**.

Usually the onset of vertigo is fairly abrupt, although some patients describe a prodromal period of several hours or days in which they felt off balance. Persistence of the symptoms for a day or more differentiates the disorder from Ménière disease. The vertigo is severe as a rule and is associated with nausea and vomiting, tinnitus is usually absent, and hearing is not affected—unlike Ménière disease (below). The severe vertigo and associated symptoms subside in a matter of several days, but lesser degrees of these symptoms, made worse by rapid movements of the head, may persist for several weeks or months.

Corticosteroids probably help recovery. More studies are needed to confirm this effect. If steroids are not used, treatment is **symptomatic** only. During the acute stage, antihistamine drugs (e.g., promethazine, clonazepam, and scopolamine) may be helpful in reducing the symptoms.

Aminoglycoside Toxicity

Aminoglycoside toxicity can cause some initial sensorineural **hearing loss** and, later, intermittent mild vertigo.

Ménière Disease

Ménière disease is characterized by recurrent attacks of vertigo associated with intermittent tinnitus that begins between 20 and 40 years of age. The characteristic triad is episodic **vertigo** (often associated with nausea and vomiting) and **tinnitus** with development of low-frequency **hearing loss** after recurrent episodes. It usually begins unilaterally but can become bilateral in 20–30% of patients.

The main pathologic changes consist of an increase in the volume of endolymph and distention of the endolymphatic system (endolymphatic hydrops), partly related to salt intake.

Diagnosis is clinical. Audiometry can help determine if hearing loss has occurred. If hearing loss is present at diagnosis, exclude neurosyphilis as a cause by checking a serum VDRL or RPR.

Antihistamines, antiemetics, and sedatives are used in acute episodes. Chronic treatment includes eradicating caffeine and reducing the intake of salt, alcohol, nicotine, and monosodium glutamate. Thiazide diuretics are used when spells continue after dietary modification. 95% of patients get their disease under control and function normally. For medically recalcitrant Ménière disease, endolymphatic sac surgery, surgical labyrinthectomy, and vestibular nerve sections remain therapeutic options.

Vertebrobasilar TIAs

Vertebrobasilar TIAs (transient ischemic attacks) may cause **intermittent**, **recurrent** vertigo. This posterior circulation TIA is usually easy to diagnose because it also causes other symptoms of **vertebrobasilar insufficiency**, such as **bilateral** vision loss, diplopia, dysarthria, **ataxia**, and bilateral extremity motor or sensory dysfunction. And, the patient usually has risk factors for stroke.

Workup of the posterior circulation requires special imaging. Know: The standard workup of looking at only the anterior circulation does **not** catch stenoses in the **posterior** circulation. In 2012, the recommended testing for imaging of the posterior circulation is **CT** or **MR angiography**. Know that duplex Doppler ultrasound is **not** recommended for these vessels because of a lack of sensitivity.

TINNITUS

Know the causes of tinnitus:

- Pulse synchronous tinnitus with IIH
- Intermittent tinnitus with Ménière's
- Aspirin overdose
- High noise levels
- Hearing loss

The tinnitus that occurs with hearing loss is thought to be a compensatory reaction to the hearing loss itself. Note that **no** tinnitus occurs with vestibular neuritis.

SEIZURES

OVERVIEW

Convulsion is an intense paroxysm of involuntary repetitive muscular contractions, and it does not always have to be present during seizures. **Seizure** is preferable as a generic term because it includes all paroxysmal electrical discharges of the brain that cause loss of consciousness; alteration of perception or impairment of psychic function; convulsive movements; disturbance of sensation; or some combination thereof. **Epilepsy** is defined as a condition of recurrent unprovoked seizures. The condition of prolonged or repetitive convulsive seizures is termed **status epilepticus** and may threaten life.

GENERALIZED vs. FOCAL

Seizures arise from the cerebral cortex.

The 2010 International League Against Epilepsy (ILAE) International Classification of Epileptic Seizures now categorizes seizure disorders into **generalized** and **focal** (previously partial):

- Generalized seizures involve both hemispheres of the brain and result in diminished consciousness. Any motor activity generally involves both sides of the body (but not necessarily).
- Focal (or partial) seizures involve one side of the brain. These are noted for motor activity on one side of the body (usually) and **no** impairment of consciousness.

Focal seizures are more commonly due to focal brain lesions while primary generalized seizures are more commonly genetic (although there are many exceptions to this rule of thumb). Previous terminology called focal seizures "partial," and, because this is a new terminology change, you will still see it listed that way for some years. So know both. Focal = Partial.

Previous categorizations had partial seizures further divided into **simple** partial (consciousness is maintained) and **complex** partial (consciousness is impaired). The newer categorization drops the "complex" term. Now you simply note how much impairment of consciousness is seen with the focal seizure.

It is also important to consider whether the seizures are primary (idiopathic) or secondary.

SEIZURE AURA

An aura is a perceptual disturbance that may precede a **focal** seizure. Auras do **not** occur with **primary** generalized seizures. Note that auras do occur with migraine, but all discussion here is in reference only to seizures.

Auras have various manifestations affecting the **senses**. They can be somatosensory perceptions such as pain, numbness, or tingling or related to other senses. They can be mostly **motor** ranging from tremors or shaking to gross motor movement. They can also be:

- Visual with lights, patterns, seeing objects
- Auditory with voices, noises, tones, and other sounds
- Olfactory with usually a burnt rubber smell
- Gustatory with the perception of strange tastes

Know: Auras, in this context (seizures), have been used as a warning manifestation of seizure and have allowed the patient to take precautions. These auras are thought to be produced by **early** seizure activity.

A focal seizure may evolve into a focal seizure with diminished consciousness, and either of these may evolve secondarily into a generalized seizure. In any of these situations, the preceding seizure is also called an aura by some.

COMMON SEIZURE TYPES

The discussion here addresses 4 main types of seizures:

- 1) **Generalized tonic-clonic** seizures are also known as a grand mal in older epilepsy literature. These involve both hemispheres, with resulting bilateral motor involvement. Consciousness is impaired with a pronounced postictal period. These seizures can be generalized from the start, or they can be focal seizures with secondary generalization.
- 2) **Absence** seizures are a type of **generalized** seizure that used to be called petit mal. These are non-convulsive, generalized seizures with **no aura** and **no postictal** symptoms. The attacks occur without warning and consist of a sudden interruption of consciousness during which the patient stares and briefly stops talking or ceases to respond. They can be induced by hyperventilating. Absences have a characteristic 3-per-second spike and wave pattern on EEG. 2/3 of affected children outgrow absence seizures.
- 3) **Focal** (or simple partial) seizures originate in a small area of the cortex. Consciousness is preserved. The symptoms of a focal seizure depend on the region of cortex from which the event is generated. For instance, a focal seizure arising in the occipital lobe (visual cortex) may be manifested by complex visual hallucinations; e.g., spinning colorful spheres.

Quick Quiz

- What are some differences between generalized and focal seizures?
- Name some environmental triggers for seizures in susceptible people.
- What is the treatment of status epilepticus?
- Which drug is used to treat absence seizures?

Jacksonian seizures are focal seizures that involve the motor strip. There may be transient, postictal paralysis of affected limbs.

- 4) **Focal seizures with diminished consciousness** (or complex partial seizures) have many causes. A common type is the **temporal lobe** seizure. In this, the preceding aura may be a hallucination or perceptual illusion. There is a period of altered behavior and consciousness, for which the patient is later found to be amnesic. The motor components of the temporal lobe seizure take the form of **automatisms**; e.g., lip-smacking, chewing or swallowing movements, salivation, fumbling of the hands, or shuffling of the feet.

Status epilepticus is defined as a seizure lasting > 30 minutes or a series of 2 or more seizures without regaining consciousness in between. It is considered a medical emergency. A cause can be determined about 2/3 of the time. Usual causes in adults include stroke, alcohol or other drugs, stopping or changing seizure medications, hypoxia, CNS infection, metabolic causes, tumor, and trauma.

Triggers for seizures in susceptible people include alcohol, cocaine, intense emotions, strobe lighting, loud music, stress, menstruation, and lack of sleep.

SEIZURE MANAGEMENT

History

When obtaining the history, check for **alcohol** or **drug** use, head injury, sleep deprivation, diabetes, and thyroid or parathyroid surgery.

Scans and Lab

Lab tests should include glucose, sodium, calcium, magnesium, LFTs, and BUN. If there are any meningeal symptoms, do a lumbar puncture and include a VDRL on the CSF studies. Order either an MRI with gadolinium or a CT with contrast after the first seizure to exclude a structural abnormality; **MRI** is almost always the best neuroimaging test. Neuroimaging is normal in classic childhood absence seizures and certain genetic epilepsy syndromes. An **EEG** showing epileptiform spikes (+/- following a slow wave) confirms the diagnosis of

seizure and may localize the origin of the seizures. A **normal EEG never** excludes the diagnosis of epilepsy.

After an initial seizure, the **risk of recurrence** is increased when there is an abnormal EEG, history of a prior neurologic injury, family history of seizures, the first seizure is a partial seizure, and/or when the MRI reveals an abnormality. In approximately 70% of all patients with epilepsy, the seizures are controlled completely or almost completely by medications; in an additional 20–25%, the attacks are significantly reduced in number and severity.

Acute Treatment of Seizures

Acute treatment of seizures: Intravenous benzodiazepines (diazepam, lorazepam, midazolam) are the drugs of choice. Phenytoin also is effective, but it takes longer to infuse. Alcohol withdrawal seizures are usually treated acutely with IV benzodiazepines or phenytoin (again, benzodiazepines first).

Typical treatment of status epilepticus in the adult: Give **thiamine** and then **D₅₀** 50 mL if the rapid glucose test is low; then benzodiazepine (**lorazepam** preferred x 2 doses) followed by a loading dose of **phenytoin** or equivalent fosphenytoin.

Fosphenytoin lacks the injection site necrosis and cardiac rhythm complications of intravenous phenytoin infusion **but** is much more expensive and may result in lower initial brain phenytoin levels, based on the time required for conversion from fosphenytoin to phenytoin. Nevertheless, it is popular in the Emergency Department. If the patient is still seizing, give a third dose of lorazepam, maximize the phenytoin dose, and then proceed to a barbiturate (phenobarbital or pentobarbital). ICU settings are generally needed if seizures are not controlled by the first 2 doses of lorazepam and a dose of phenytoin.

Chronic Treatment of Seizures

Antiepileptic drugs (AEDs) are the mainstay of treatment, with **monotherapy** the preferred goal (Table 11-2). The choice of antiepileptic drug depends primarily on the seizure type, with additional considerations including cost, side-effect profile, and patient preference for a dosage schedule. Usually, drugs are not started until a patient has suffered at least 2 seizures.

Partial seizures: **Almost all** available AEDs are effective in the treatment of partial seizures. The notable **exception** is **ethosuximide**, an agent that is used to treat only absence seizures. With few exceptions, the AEDs are considered equally effective. The main differences are that the older AEDs are generally cheaper; however, the newer ones are generally better tolerated and have fewer side effects.

Generalized seizures: The list of effective agents for generalized seizures is shorter, and includes:

- Valproate
- Lamotrigine
- Topiramate
- Levetiracetam
- Felbamate
- Rufinamide
- Zonisamide

When can you **stop** the medication? This must be individualized. Risk factors include a seizure within the last 2 years, epileptiform spikes on the EEG, abnormal MRI, and a late age of onset of the seizures.

Know also that certain AEDs **reduce** the efficacy of **oral contraceptive** pills:

- Phenytoin
- Phenobarbital
- Carbamazepine
- Felbamate
- Topiramate
- Oxcarbazepine

Women taking these AEDs should use a method of birth control other than oral contraceptives. Note: Oral contraceptives can **increase** the drug concentration of the AED **lamotrigine**.

Many of the drugs mentioned above are also **teratogens**, hence, the importance of knowing their effect on oral contraceptives. The teratogens include: phenytoin, phenobarbital, carbamazepine, topiramate, and valproic acid. (See Treatment of Seizures During Pregnancy next.)

Options for intractable epilepsy include resective surgery (best for temporal lobe epilepsy), vagus nerve stimulation (doesn't work as well as surgery), and the ketogenic diet (works well in children).

Driving restrictions vary from state to state and continue to evolve. The Epilepsy Foundation has updated information for your state: www.epilepsyfoundation.org.

Treatment of Seizures During Pregnancy

[Know!]

The background risk for birth defects is 2–3%. The goal of treatment during pregnancy is to control the seizures—uncontrolled seizures can cause placental abruption and early labor and premature delivery. When the risk of teratogenicity is compared to the problems that seizures cause during pregnancy, the risks of uncontrolled seizures is **greater!**

Maintain a pregnant woman on **monotherapy** at the **lowest dose** of medication possible; risk of malformations increases as each drug is added.

There is no “safe” AED, but **valproate** is **more** likely to cause **neural tube** defects than other commonly used antiepileptics. The teratogenic risk of AEDs is **decreased** by **folic acid**, and thus, all women of childbearing age on antiepileptic drugs should take 1–2 mg of folate daily.

Table 11-2: Notable Advantages and Disadvantages of Antiepileptic Drugs (AEDs)

Drug	Used to Treat	Notable Advantages/Disadvantages
Phenytoin	Partial (1) Generalized tonic-clonic (alternative)	Good: long half-life so dose 1–2x/d Bad: gum hyperplasia, hirsutism, coarsening of features, lymphadenopathy, osteomalacia; toxicity may present at near-normal concentrations; teratogenic
Carbamazepine	Partial (1) Generalized tonic-clonic (alternative)	Good: Toxicity is uncommon. Bad: hyponatremia, leukopenia, thrombocytopenia, aplastic anemia, hepatotoxicity, teratogenic
Valproic acid	Generalized tonic-clonic (1) Absence (alternative) Partial (alternative, esp if it generalizes)	Bad: GI side effects (less with Depakote® formulation); may rarely cause bone marrow suppression and hepatotoxicity/liver failure; teratogenic (neural tube defects)
Ethosuximide	Absence (1) only	Bad: may cause bone marrow suppression (rare)
Lamotrigine	Partial (adjunctive use)	Bad: may cause severe rash and Stevens-Johnson syndrome
Gabapentin	Partial (adjunctive use)	Good: the only one with no significant drug interactions; renal clearance so it is useful in those with liver disease Bad: ataxia, amnesia
Clonazepam	Absence (short-term adjunctive use only)	Bad: loses efficacy
Phenobarbital	Partial (last choice)	Bad: sedation in adults, hyperactivity in children, among other cognitive changes; teratogenic

Note: (1) = **primary drug** **Note:** Any of the above AEDs can cause ataxia, dizziness, and somnolence.

Quick Quiz

- Which AEDs decrease the effectiveness of oral contraceptives?
- What is the classic triad of symptoms observed in patients with a brain abscess?
- How does treatment of a varicella infection differ from the treatment of herpes simplex?
- What is the diagnostic test for West Nile virus encephalitis?

Physicians generally give prophylactic **vitamin K** during the last **month** of pregnancy in patients on AEDs, based on reports indicating increased bleed in patients on AEDs. However, most recent guidelines say there is not enough evidence to recommend for or against use of prophylactic vitamin K.

INFECTIONS

BACTERIAL CNS INFECTIONS

Acute Meningitis

Diagnose with analysis of the cerebrospinal fluid (CSF). If there are focal neurologic signs or papilledema, do a CT before the lumbar puncture (LP). CSF latex agglutination tests are no longer recommended in the **initial** evaluation of meningitis; they test for *H. influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *E. coli* and *Streptococcus agalactiae*. With suspected meningitis, start antibiotics immediately **after** the LP and blood cultures; do **not** wait for any LP results. Also, if doing the LP is going to be delayed more than 30–60 minutes, go ahead and give antibiotics immediately (before the LP)! Further discussion and treatments are featured in the Infectious Disease section, Book 1.

Neurosyphilis also is discussed in the Infectious Disease section, Book 1.

Brain Abscess

The classic triad of symptoms is **headache**, **fever**, and **focal neurological deficit(s)**. Most abscesses arise from intracranial extension of cranial infections (sinuses, teeth) or after skull fracture or neurosurgical procedures. Much less often, they are due to bacteremic seeding. In adults, the most common organisms are **staph** and **strep** species (e.g., *S. epidermidis* after a penetrating head injury), but don't forget about *Nocardia*. In the immunocompromised, consider toxoplasmosis.

VIRAL CNS INFECTIONS

CSF in Viral Encephalitis

With viral encephalitis, CSF has increased **lymphocytes**, normal to slightly increased **protein**, and normal glucose. **EEG** is almost always abnormal with diffuse slowing or **focal temporal** changes. The MRI is more sensitive than CT and may show hemorrhagic changes.

Herpes Simplex Encephalitis

Herpes simplex encephalitis is the most common type of **non-epidemic** viral encephalitis. In adults, it is usually due to a reactivation of the HSV-1 virus, although 25% are due to primary HSV-1 infection. HSV-2 is sexually transmitted and can cause aseptic meningitis during primary infection. HSV-2 less commonly causes encephalitis but can cause polyradiculitis and myelitis.

Varicella zoster virus (VZV) can also cause encephalitis, especially in the immunocompromised; and, it is associated with vesicular lesions that can be confused for herpes simplex. It's important to think about VZV because the dose of acyclovir required to treat is higher.

Treat herpes encephalitis with IV **acyclovir** and assume it is caused by VZV until you can exclude. (So, use higher initial doses of acyclovir.) Much more on herpes is covered in the Infectious Disease section, Book 1.

Mosquito-Borne Arboviruses

If mosquitoes are around, think about arboviruses, especially **eastern/western equine** and **St. Louis encephalitis** viruses. **West Nile virus** tends to cause encephalitis only in the older patients with comorbidities and in the immunocompromised. (It causes "West Nile fever" in younger and healthy patients.)

Diagnosis of Viral Encephalitis

Polymerase chain reaction (**PCR**) DNA amplification of the herpes viruses now allows for an easy, rapid, and accurate diagnosis of herpes simplex and zoster.

Acute and convalescent **serum** titers are drawn to diagnose most **arboviruses**.

West Nile diagnosis requires finding **antibody** in **spinal fluid**.

Viral **culture** of spinal fluid is useful to identify most other causes of simple viral meningitis/encephalitis.

Viral Myelitis

Myelitis is infection of the spinal cord—a classic viral cause is **poliomyelitis**! Usually this presents as "transverse myelitis," meaning it affects a transverse segment of the cord. Common causes today are other **enteroviruses** (coxsackie and enterovirus) and **flaviviruses**, such as West Nile. Other forms of myelitis (less segmental) can be caused by **herpes simplex**, **varicella zoster**, and **Epstein-Barr**.

Slow Viruses and Prions

Slow viruses:

- Subacute sclerosing panencephalitis (SSPE) is caused by the measles virus; most cases occur around age 10, many years after the initial infection.
- Progressive multifocal leukoencephalopathy (PML): See below and also under Demyelinating Diseases on [page 11-38](#).

Prion: Creutzfeldt-Jakob disease (CJD) (See under Dementia, on [page 11-10](#).)

HIV

Infection with HIV can result in dysfunction of **any** part of the nervous system. Patients get subacute encephalitis, peripheral neuropathies including mononeuritis multiplex, vacuolar myelopathy, and aseptic meningitis.

HIV-associated cognitive impairment is common. It ranges from asymptomatic to mild to what is called HIV-associated dementia (HAD). In adults, it takes the form of a slowly or subacutely progressive dementia with loss of retentive memory, inattentiveness, language disorder, and apathy.

Know that the differential diagnoses include progressive multifocal leukoencephalopathy (below), toxoplasmosis (below), and lymphomas.

Since the use of ART began, the incidence (new cases per year) of HAD in the U.S. has dropped by half. Patients are getting a different type of dementia post-ART; this dementia is associated more with deficits in complex reasoning and less with global impairment. In addition, even though the incidence is dropping, HAD is occurring in patients with higher CD4 counts, even in patients who have had long-term viral suppression on antiretroviral agents.

Poliomyelitis is more likely to occur in AIDS patients. Differentiation between AZT myopathy and poliomyelitis may require a muscle biopsy.

Peripheral AIDS neuropathy has 3 forms:

- 1) In chronic inflammatory demyelinating polyneuropathy, there is progressive weakness of the legs and loss of deep tendon reflexes. There is a high protein level and a high cell count in the patient's CSF. Treatments are corticosteroids, IVIG, and plasmapheresis—all equally effective.
- 2) Distal symmetric polyneuropathy is common in AIDS patients (1/3 get it). Symptoms are paresthesias of the feet and distal weakness in the legs. Treatment usually includes tricyclic antidepressants or gabapentin.
- 3) A painful mononeuritis multiplex thought to be due to focal vasculitis also occurs.

Progressive multifocal leukoencephalopathy (PML); affects **white** matter only) is usually seen in patients with **T-cell** immune defects (HIV/AIDS, chronic steroids, monoclonal antibodies) and chronic **neoplastic** diseases. In addition, we are now seeing cases of PML in patients taking a number of **immunosuppressants** for treatment of rheumatologic, hematologic, and inflammatory bowel diseases (rituximab, fludarabine, mycophenolate, chronic corticosteroids), and with a newer drug to treat multiple sclerosis, natalizumab.

PML is caused by the human **JC polyomavirus**, resulting in a progressive demyelination of the CNS white matter.

Symptoms are varied and usually start with abnormal mentation (personality changes and intellectual impairment) and then slurred speech. A combination of hemiparesis progressing to quadriparesis, visual field defects, cortical blindness, aphasia, ataxia, dysarthria, dementia, confusional states, and coma are seen. Some patients have a predominantly cerebellar syndrome.

Diagnose with brain biopsy. Finding JC virus in the CSF by PCR is supportive, although this occurs less often in patients with PML being treated with ART.

Vacuolar myelopathy (see Infectious Myelopathies—AIDS on [page 11-29](#)) causes progressive weakness, incontinence, hyperreflexia, and ataxia. There is vacuolation and deterioration of the dorsal and lateral spinal columns. It is uncommon. This myelopathy must be differentiated from B₁₂ deficiency and from spinal cord compression due to some other cause, such as lymphoma.

PARASITIC CNS INFECTIONS

Toxoplasmosis

AIDS-related brain lesions: If you see **multiple ring-enhancing lesions**, think **toxoplasmosis**. (CNS lymphoma, TB, and bacterial infections are less likely.)

Because toxo is a **reactivation** infection, patients usually have **IgG** (but not IgM) antibody to *T. gondii*. But many people have toxo antibodies, so a positive toxo IgG is only supportive and not diagnostic. Also know that an absent toxo IgG does **not** exclude toxoplasmosis as the cause of a brain lesion in an AIDS patient.

Treat with sulfadiazine, pyrimethamine, and leucovorin. Add dexamethasone if there is midline shift or rapid deterioration.

Do a brain biopsy if there is no improvement after empiric treatment, if there is a mass effect, or if there is only 1 lesion. Some empirically treat single lesions if the CD4 count is < 100 and the patient hasn't been on toxo prophylaxis. Relapses occur often.

Neurocysticercosis

Neurocysticercosis is the **most common worldwide parasitic** CNS infection. It is caused by ingesting food or water contaminated with *Taenia solium* (a tapeworm).

Quick Quiz

- Aside from patients with AIDS, PML can occur in which patients? What are symptoms?
- What is the treatment for CNS toxoplasmosis?
- What is the clinical presentation of neurocysticercosis?
- Characterize the CSF of a patient with cryptococcal meningitis.
- Which viral infection recently has been associated with subsequent stroke?
- In addition to exercise, smoking cessation, and control of diet, blood pressure, and lipids, what other interventions should be offered to certain patient groups in order to prevent stroke?

It forms cysts in the brain, which initially cause no symptoms. But when the cyst walls break down several years later, it causes cerebral edema, usually with **seizures** as the first symptom. In some patients, a large subarachnoid or intraventricular cyst may obstruct the flow of CSF. In a more malignant form of the disease, the cysticerci are located in the basilar subarachnoid space, where they induce an intense inflammatory reaction leading to hydrocephalus, vasculitis, and stroke as well as cranial nerve palsies.

MRI is the preferred imaging modality—when worms are viable, MRI shows multiple, **non-enhancing** hypodense lesions. As the worms die, they are surrounded by edema and flair. When dead, they calcify and shrink. Support the diagnosis with *T. solium* antibody testing on serum.

Treatment of CNS infection is controversial because of both the lack of randomized studies and the propensity of dying worms to cause symptoms. Most experts now treat with high-dose praziquantel or albendazole +/- corticosteroids. AEDs are given to patients at high risk for seizures. More about this infection in the Infectious Disease section, Book 1.

FUNGAL CNS INFECTIONS

Cryptococcal Meningitis

Especially consider cryptococcal meningitis when working up a progressive headache, cognitive impairment, and/or meningeal signs in patients with AIDS or on chronic corticosteroids. CSF pressure is usually **very elevated**. Standard CSF studies can be entirely normal, so always check the **cryptococcal antigen titer** in the blood and CSF.

Treat with amphotericin B deoxycholate or liposomal amphotericin B and flucytosine x 2 weeks, then change to oral fluconazole x 8 more weeks (minimum). Lower doses of oral fluconazole are required for secondary prophylaxis

in immunosuppressed patients. Manage elevated intracranial pressures with daily taps to keep CSF pressure < 200 mm H₂O, or patients can lose their vision. Shunts are appropriate if daily taps are needed. Do not use mannitol, acetazolamide, or corticosteroids. More about this infection in the Infectious Disease section, Book 1.

STROKE

OVERVIEW

Stroke, after heart disease and cancer, is the third most common cause of death in the U. S. The term **stroke** is applied to a sudden focal neurologic syndrome caused by cerebrovascular disease. **Cerebrovascular disease** refers to an abnormality of the brain caused by pathology of blood vessels such as:

- **Occlusion** by embolus or thrombus
- Vessel **rupture**
- Altered **permeability** of the vessel wall
- Increased **viscosity** or other change in the quality of the blood flowing through the cerebral vessels

The primary vascular disorder may be atherosclerosis, hypertensive arteriosclerotic change, arteritis, aneurysmal dilatation, or a developmental malformation. The secondary parenchymal changes in the brain resulting from the vascular lesion could be ischemia, with or without infarction, and hemorrhage.

Know that varicella zoster infection has been identified as a risk factor for ischemic and hemorrhagic strokes and TIA (increases risk by 30%), especially if the presentation is herpes zoster ophthalmicus.

Brain ischemia **without infarction** has been recently defined by the American Stroke Association as a transient ischemic attack (**TIA**). **Stroke** has been defined as **infarction** and may result in temporary or permanent cognitive, motor, and/or sensory deficits.

Note that the latest guideline on TIA from the American Stroke Association has **removed** all references to **duration** of symptoms. The definition was changed because true infarction sometimes occurs even when symptoms last less than 24 hours, making the previous definition of TIA occasionally incorrect.

Strokes are classified as **ischemic** or **hemorrhagic**. Ischemic strokes can be thrombotic or embolic.

PRIMARY PREVENTION OF STROKE

2010 guidelines for **primary** prevention of stroke include:

- Treatment of blood pressure and lipids (per guidelines)
- Smoking cessation
- Diet and exercise

- Treatment of atrial fibrillation with anticoagulation based on national guidelines (see the Cardiology section on A. fib, Book 3) using any of the following:
 - Aspirin
 - Warfarin
 - Aspirin + clopidogrel (in patients unable to tolerate warfarin)
- Carotid endarterectomy if > 70% stenosis
- Prophylaxis for migraine (previously discussed on [page 11-5](#))
- Evaluation and treatment of obstructive sleep apnea
- Screening for aneurysms with CTA or MRA for the following:
 - Patients who have **2 or more** 1st degree relatives with SAH/aneurysm (but screening is **not** recommended in patients who have only **one** affected 1st degree relative)
 - Patients who have autosomal dominant polycystic kidney disease (**ADPKD**) and **1 or more** relatives with ADPKD + SAH/aneurysm

IMAGING OF STROKES

In 2009, the American Heart Association published recommendations for how best to image patients with possible stroke, based on an extensive literature review and specialty consensus publications. The recommendations focus on the best use of CT and MRI. A main reason to do neuroimaging is to determine whether a patient is eligible for tissue plasminogen activator (**t-PA**), but there are other uses:

- Exclude intracerebral (ICH) or subarachnoid hemorrhage (SAH)
- Detect ischemia
- Exclude other illnesses that present as stroke
- Image the vessels
- Assess possible viability of infarcted tissue

Imaging with CT: A **non-enhanced** CT (**NECT**) scan can be performed as a basic form of stroke imaging ([Image 11-3](#)). The NECT can be enhanced by adding either of the following:

- Angiography (CTA)
- Dynamic perfusion studies (CTP)

When adding angiography, evaluation of source images (SI) helps to interpret the study (CTA-SI).

Imaging with MRI: MRI can also be enhanced using additional imaging sequences:

- Diffusion weighted imaging (DWI)
- Perfusion (MRP)
- Angiography (MRA)

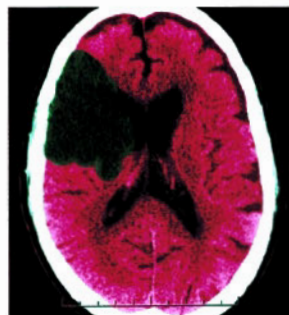


Image 11-3: CT of MCA stroke

- Gradient-recalled echo (GRE)
- Fluid-attenuated inversion recovery (FLAIR)

The CT and MRI enhancements help to better accomplish the purposes of imaging. Usually most, if not all, of these sequences are performed **whenever** you order an MRI of the brain. In the best circumstances, a CT scan with enhancements takes the same amount of time as an MRI with enhancements. For example, it takes 10 minutes to do either NECT with CTA/CTA-SI and dynamic CTP or MRI with FLAIR, GRE, MRP, and intracranial MRA! The major problem today is that not all hospitals provide access to the MRI scanner for triage situations. In many Emergency Departments, only CT is available.

Now that you know the abbreviations and acronyms, we'll go over which imaging to use in particular situations:

- Intracerebral hemorrhage (ICH): MRI-GRE is **equivalent** to NECT for finding blood. We used to believe that CT was better, but many studies now show that it is not. MRI is also better for detecting hemorrhagic transformation of ischemic stroke.
- Subarachnoid hemorrhage (SAH): Use NECT. MRI with FLAIR is probably as good as NECT, but as of early 2012, we do not have any direct comparison studies.
- Ischemia: MRI-DWI is best. CTA-SI is comparable, but it is not as good for imaging of the posterior fossa/brain stem and for discovering small infarcts. MRI is also better than NECT to detect an occluded vessel.

Because of the above, unless your patient has signs and symptoms of SAH, MRI + DWI and MRI + GRE sequences (at minimum) are the best imaging for possible ischemic stroke, because they both exclude ICH and identify areas of infarction—provided you can get the test without delay. Remember that time from symptom onset > **4.5 hours** precludes use of t-PA (< 3 hours best). If you cannot get an MRI in a reasonable time frame, then get a CT with CTA-SI.

CTA or MRA is recommended to evaluate the intra- and extracranial vasculature of patients with **TIA** or **stroke** symptoms. Both imaging modalities are significantly more sensitive and specific than carotid Doppler ultrasound for diagnosing extracranial vascular stenosis. Carotid ultrasound also tends to **overdiagnose** lesions and leads to unnecessary surgery in some patients. CTA is better than MRI at identifying intracranial aneurysms.

If performing CTA or MRA doesn't extend the time period from symptom onset out past **4.5 hours** maximum (< 3 hours best), either is recommended as part of the **initial** evaluation of stroke because, sometimes, clotted vessels can be treated with urgent intraarterial therapy or stents. Patients with a large clotted

Quick Quiz

- What imaging study would you do for a patient with a suspected SAH?
- Which imaging study is best to evaluate the anterior carotid and posterior circulations in patients with TIA or stroke?
- How does a patient with an ACA stroke typically present?
- How does a patient with an MCA stroke typically present?

vessel—often the MCA, so-called “hard thrombus”—do not respond as well to t-PA as direct intervention.

Although assessing viable brain tissue after infarction is one of the main purposes for imaging a stroke patient, we are still in the beginning stages of learning how to incorporate the data into treatment plans. Dynamic CTP and MRP are the leading imaging techniques.

ISCHEMIC STROKES

Thrombotic vs. Embolic Strokes

Thrombotic strokes: Atherosclerotic occlusion is most common in the internal carotid, middle cerebral, vertebral, and basilar arteries.

The initial neurologic symptoms often occur in a slow, stepwise progression (termed “stroke in evolution”). Often patients have a history of TIAs in the same distribution as the presenting symptoms of their stroke. If the patient has not had TIAs, a clear differentiation between thrombotic and embolic may be difficult. Other, rarer causes of thrombotic occlusion are lupus anticoagulant, polycythemia, meningovascular syphilis, dissecting aortic aneurysm, and thrombocytosis.

Embolic strokes: Neuro deficit is usually **worst at onset**. Embolic strokes usually are **not** preceded by a **TIA**. Emboli from the heart usually go to the middle > posterior > anterior cerebral arteries. Emboli can also be multiple.

Anterior Circulation

Anterior Cerebral Artery (ACA) Strokes

When the ACA is affected distal to the anterior communicating artery, the weakness and sensory loss affect primarily the contralateral leg.

Urinary incontinence and gait abnormalities may also be present. If the **corpus callosum** is affected, patients may develop “tactile agnosia,” which is an inability to recognize objects by touch.

Occlusion of the stem of the ACA, proximal to the anterior communicating artery is usually well tolerated because collateral flow is provided by the other ACA. When both arteries arise from one stem, there is resulting paraplegia, incontinence, lack of motivation (termed “abulia”), and frontal lobe personality changes.

Buzz phrase: The patient with the **ACA** stroke typically presents with **leg weakness** that is **opposite** to the side of the stroke.

Middle Cerebral Artery (MCA) Strokes

Most MCA stem occlusions are from **emboli**. MCA strokes result in **contralateral weakness** (“hemiplegia”) which is denser if the internal capsule is involved, **sensory loss** (“hemianesthesia”), and a **homonymous hemianopsia**. If the **dominant** hemisphere is involved (the **left** side in most people, even left-handed individuals), these patients experience **aphasia**.

A lesion that affects the lower part of the left frontal lobe (Broca’s area) causes **expressive** (or **Broca**) **aphasia**. These patients understand language, but they have trouble forming words and sentences, so their speech is non-fluent and effortful. A lesion at the boundary of the temporal and parietal lobes causes a “**fluent**” or “**sensory**” aphasia, called **Wernicke** aphasia. These patients can’t comprehend written or spoken language and have errors in their spontaneous speech, often speaking in invented words, termed “**neologisms**.” An extensive infarction may produce “global aphasia,” which is both expressive and sensory. If the non-dominant hemisphere is involved, patients may experience changes in spatial perception and may develop hemineglect syndrome.

With parietal lesions of either hemisphere, “cortical” sensory signs are often present: contralateral loss of 2-point discrimination, failure to perceive tactile stimuli on the opposite side of the involved hemisphere when stimuli are presented to both sides simultaneously (termed “sensory inattention”), tactile agnosia, and an inability to recognize letters drawn on their palm (termed “**agraphesthesia**”).

If the lesion involves the frontal lobe, patients may have a gaze preference or gaze deviation—they look toward the side of the lesion for 1–2 days after the stroke.

Buzz phrases: The patient with the **MCA** stroke typically presents with **garbled speech** and **arm/leg weakness** that is **opposite** to the side of the stroke.

Posterior Circulation

Posterior Cerebral Artery (PCA) Stroke

PCA strokes usually cause contralateral homonymous hemianopsia—usually a superior quadrantanopsia with temporal lobe lesions, an inferior quadrantanopsia with parietal lobe lesions, or a homonymous hemianopsia with medial occipital lesions. There may be

mild contralateral sensory loss, inability to name colors (termed “color anomia”), failure to see to-and-fro movements, inability to count objects, inability to fixate on points in peripheral visual fields (termed “ocular apraxia”), inability to see more than one object at a time if the dominant occipital lobe is involved (termed “simultanagnosia”), visual hallucinations and/or memory loss.

If the patient has anomia for colors, the posterior aspect of the corpus callosum (splenium) may have been affected.

If disruption of blood flow occurs bilaterally, the memory loss is severe and persistent.

Bilateral cortical blindness may result from simultaneous or successive posterior cerebral artery occlusion but may also be due to anoxia related to surgery, especially cardiac surgery. Occasionally, patients with cortical blindness deny their visual defect (Anton syndrome).

Buzz phrase: The patient with **PCA** stroke typically presents with **visual** field defects + **color** blindness + **paresthesias** without any motor findings.

Single Hemisphere Strokes

Single hemisphere strokes usually do not affect paraspinal muscles or muscles of the pharynx, jaw, and forehead. If these muscles are affected, think bilateral hemispheric involvement or brainstem stroke (below). Remember: Upper motor neuron lesions of cranial nerve 7 do **not** affect eye closure or forehead wrinkling, which helps you clinically to distinguish between a **central** lesion and Bell’s palsy (**peripheral** 7th nerve involvement).

Vertebral / Basilar Artery Occlusion

Vertebral and/or basilar artery occlusion is the usual cause of **brainstem** strokes. That the problem involves the **posterior circulation** delivering blood to brainstem (posterior fossa) structures is suggested by the following:

- Bilateral extremity motor and sensory dysfunction (quadriplegia in severe cases)
- “Crossed” sensory findings (e.g., right face, left arm)
- Horner syndrome
- Cerebellar signs
- Stupor and coma
- Cranial nerve dysfunction not usually affected by single hemisphere strokes (diplopia, pharyngeal weakness, jaw weakness, and deafness)
- Crossed hemiplegias (e.g., ipsilateral cranial nerve deficit and contralateral arm or leg weakness)

A **vertebral stroke** may cause **lateral medullary syndrome** (also called **Wallenberg syndrome**), which has a **mixed bag** of symptoms [Know]:

- Ipsilateral cerebellar signs and symptoms (due to involvement of the inferior cerebellar peduncle and cerebellum)

- Nausea, vomiting, nystagmus (vestibular nuclei)
- Ipsilateral Horner syndrome (due to involvement of the descending sympathetic fibers)
- Ipsilateral palate and vocal cord weakness (involvement of the nucleus ambiguus)
 - “**Crossed**” sensory loss (ipsilateral face and contralateral body, due to involvement of the trigeminal nucleus and tract and spinothalamic tract, respectively)

Buzz phrases: The patient with the **posterior circulation** stroke typically presents with:

- Vertigo and diplopia if due to vertebrobasilar artery; sometimes with antecedent TIA symptoms
- Lateral medullary syndrome (defined above)
- Vertigo + nystagmus + nausea + ataxia (if **cerebellar**)

(There are other brainstem infarction syndromes, but we won’t discuss them here.)

Lacunar Infarcts

Small artery disease, usually due to chronic hypertension or diabetes, can lead to small vessel occlusion with resultant necrosis of small areas of the brain. Over time, resorption of these necrotic regions causes small infarcts or “lacunae” to develop.

Although most are silent, hallmarks of **symptomatic lacunar infarcts** are:

- Pure hemiplegia (with no sensory dysfunction)
- Pure hemisensory stroke (with no motor dysfunction)
- Ataxic hemiparesis (ataxia ipsilateral to hemiparesis)
- Clumsy hand-dysarthria syndrome

Multiple bilateral frontal lobe lacunae can result in pseudobulbar palsy—emotional lability with uninhibited crying or laughter and evidence of upper motor neuron signs such as brisk jaw jerk, hyperreflexia, and Babinski sign.

Evaluation of Ischemic Stroke

The patient with a neurologic deficit should be assessed like any other emergency, using the ABCs first: stabilize **airway**, **breathing**, and **circulation**. If the patient is stable, take a good history. The most important element is the **time** of symptom **onset** because that determines eligibility for an IV **thrombolytic**. If the patient awoke with deficits, then the last time he/she remembers having normal function is the time of symptom onset. Remember that complicated migraines, postictal states, and subdural hemorrhages can resemble a stroke; so ask about headaches, seizure activity, and falls.

Physical exam focuses on possible sources and alternative diagnoses. Look for evidence of seizures (tongue biting), trauma, myocardial ischemia, carotid and vertebral artery bruits, heart murmurs, and arrhythmias.

The National Institutes of Health Stroke Scale (NIHSS) score is a standardized instrument incorporated as part

Quick Quiz

- How does a patient with a PCA stroke typically present?
- What is the clinical presentation of lateral medullary syndrome? What type of stroke causes it?
- What tests are recommended in the initial evaluation of ischemic stroke?

of a physical exam at most stroke centers. We've reproduced the general concepts of the scale in Table 11-3, but you really should study and use the full scale. A copy of the NIHSS instrument is available at www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf.

The NIHSS helps to quantify neurologic deficits, communicate with neurologists, possibly identify the occluded vessel, make an early prognosis, and identify a patient's suitability for thrombolytics. Patients get points for their inability to complete the various parts of the assessment.

Recommended diagnostic tests at presentation of possible ischemic stroke include:

- Imaging of the brain and intra/extracranial vessels (previously discussed on page 11-20)
- Basic chemistries with glucose
- CBC with platelets

- PT, PTT, INR
- 12-lead ECG ± telemetry monitoring for arrhythmias
- Echocardiogram

Optional tests: A lumbar puncture with CSF assessment should be done if SAH is a concern and NECT does not show blood. Also consider an EEG (if you suspect patient has seizures), a urine drug screen, blood alcohol, blood gas, and pregnancy test as other potentially appropriate tests.

Acute Treatment of Ischemic Stroke

If the stroke occurred < 3 hours ago and the NIH stroke scale rating is > 4, t-PA has been shown to be effective in decreasing severity or reversing neurological deficits, provided that the patient fits a specific clinical presentation (2007 stroke treatment guidelines from the American Stroke Association). The following patients should be treated with t-PA. The list also contains exclusion criteria for patients with stroke symptoms < 3 hours:

- Ischemic stroke with neurologic deficit(s) that is/are neither minor nor spontaneously improving
- No symptoms of subarachnoid hemorrhage or history of intracranial hemorrhage
- No head trauma, stroke, or myocardial infarct in last 90 days
- No GI or GU hemorrhage in last 21 days
- No major surgery in last 14 days
- No arterial punctures in last 7 days
- Systolic BP < 185 and diastolic BP < 110 mmHg
- No bleeding or trauma on exam

Table 11-3: NIH Stroke Scale

Assessment	Instructions
Consciousness: Level	Choose a response: alert, arousable by minor stimuli, requires repeated or painful stimuli, unresponsive or reflexes only, or areflexic.
Consciousness: Questions	Ask month and age. No partial credit. Aphasic and stuporous patients score 2. Intubated patients score 1.
Consciousness: Commands	Ask patient to open and close eyes, then to grip and release non-paretic hand.
Gaze	Test horizontal eye movements.
Vision	Test visual fields by confrontation with finger counting.
Facial palsy	Ask patient to show teeth or raise eyebrows and close eyes.
Motor: Arm and Leg	Test for pronator drift.
Ataxia	Perform finger-nose-finger and heel-shin tests.
Sensation	Assess for sensation or grimace to pinprick or withdrawal from noxious stimulus.
Language	Describe what is happening in a picture, name items printed on paper, and read a sentence.
Speech	Read words from a list.
Extinction and Inattention	Assess previous tests to determine if patient orients only to one side.
For the full scale with scoring, go to www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf	

- Not taking oral anticoagulation, or INR ≤ 1.7 if taking anticoagulant
- Normal PTT if received heparin in past 48 hours
- Platelets $\geq 100,000/\text{mm}^3$
- Blood glucose $\geq 50 \text{ mg/dL}$
- No history of seizures with postictal impairment
- CT area of infarct should be $< 1/3$ of middle cerebral artery territory
- Patient and/or family understand risks:benefits ratio

If **> 3 hours** but **< 4.5 hours** have elapsed, data and recommendations from the American Stroke Association (2009) say patients can still be treated with t-PA and receive benefit, provided that the following patients or situations are excluded (presence of any **one excludes t-PA**):

- Age > 80 years
- Taking oral anticoagulants, regardless of INR
- Baseline National Institutes of Health Stroke Scale score > 25
- Comorbid diabetes mellitus

For stroke symptoms present for **> 4–4.5 hours**, management is **conservative** and emphasizes supportive care and treatment of complications:

- Give airway support to stroke patients with reduced consciousness or airway compromise; oxygen prn.
- Look for and treat sources of fever. Give antipyretics to reduce fever.
- Use cardiac monitoring for first 24 hours after stroke to assess for arrhythmias.
- Treat hypertension cautiously, so as not to extend infarct size. If the patient meets criteria for t-PA except for BP, go ahead and treat to reduce BP to $\leq 185/110$; then give t-PA. If not giving t-PA, withhold meds for BP $< 220/120$ and allow the patient to gradually drop their pressure on their own. If BP $> 220/120$, then treat with the goal of reducing the BP $\sim 15\%$ in first 24 hours. Recommended meds from guidelines include IV labetalol, nitropaste, and nicardipine infusion.
- Restart antihypertensives for patients with long-standing hypertension after 24 hours (if not treated already for BP $> 220/120$).
- Maintain normoglycemia.

In patients ineligible for treatment with t-PA, and who are not taking anticoagulation for any other underlying disease, give 325 mg aspirin once followed by daily aspirin 150–325 mg/day while hospitalized. Optimal dose is not yet clear. The risk of hemorrhagic transformation of an infarct is not high enough to offset the benefits of aspirin therapy, so treat all eligible patients, even if a small hematoma is present within the infarcted area. There is no benefit to treating ischemic strokes with heparin or low-molecular-weight heparin, unless the patient meets criteria for heparin use otherwise (e.g., atrial fibrillation or a cardiac thrombus).

If the stroke occurs in the **posterior fossa**, **admit** the patient for close observation. Expansion of the contents of the posterior fossa can cause either upward or downward **herniation**; these patients then decompensate quickly and without warning.

Chronic Treatment of Ischemic Stroke

Reduce the patient's risk factors for stroke by treating hypertension, diabetes, and lipids according to national guidelines, and add either:

- Aspirin 50–325 mg/day + extended-release dipyridamole
- Clopidogrel

The combination of **ASA + ER-dipyridamole** is better than either agent alone. Use clopidogrel in patients with aspirin allergy. Know that aspirin + clopidogrel does not offer additional benefit and does increase risk of bleeding. Headache is a common side-effect of dipyridamole and sometimes causes patients to self-discontinue the drug. Usually the headaches can be treated symptomatically with acetaminophen. Do not use ticlopidine. It's expensive, performs no better than the agents above, and can cause significant neutropenia.

Anticoagulate patients with atrial fibrillation if the patient meets guidelines (see the Cardiology section on A. fib, Book 3). Refer for carotid endarterectomy if the patient has $> 70\%$ occlusion and an expected lifespan of > 5 years.

INTRACEREBRAL HEMORRHAGE

Overview

Hemorrhagic stroke is usually due to **rupture** of **small arteries**, especially when the small artery branches off at a 90-degree angle from the parent vessel and the blood pressure is very high. The 2 most common causes are **hypertension** and **amyloid angiopathy**. Warfarin use is a risk factor, especially when the **INR is > 3** .

Some patients have preexisting evidence of intermittent, small bleeds on MRI of the brain. It is possible that these MRI-visible "microbleeds" are indicators of which patients are prone to future intracerebral hemorrhage. Because the bleeding arises from small arteries, the symptoms of microbleeds typically evolve gradually but continuously.

Signs and Symptoms

Hemorrhagic stroke occurs in the following 4 areas of the brain (from **most** common site to **least** common):

- 1) Putamen and adjacent internal capsule (50%): If the hematoma involves the internal capsule, there is contralateral hemiparesis and usually sensory loss and hemianopsia. This type of hemorrhage may be difficult to distinguish from a middle cerebral artery

Quick Quiz

- What is the timeframe for prescription of t-PA in patients with ischemic stroke?
- What are the recommendations for lowering of blood pressure in patients with ischemic stroke who do not receive t-PA?
- Why should you keep a patient with an ischemic stroke in the posterior fossa under close observation?
- What are the recommended antiplatelet regimens post-stroke?
- What are the most common causes of an intracerebral hemorrhage?
- What are the recommendations for treatment of blood pressure in a patient with an intracerebral hemorrhage?
- What is the most common cause of SAH?

infarct (one of the reasons to do the enhanced NECT or MRI looking for blood at presentation). For central white matter of the temporal, parietal, or frontal lobes, symptoms are based on the lobe affected.

- 2) Thalamus: contralateral hemianesthesia without “cortical” sensory signs. Some motor signs may be present if the adjacent internal capsule is involved.
- 3) Pons: coma, pinpoint pupils, and quadriplegia. There may be decerebrate posturing bilaterally.
- 4) Cerebellum: acute dizziness, ataxia, and vomiting with no change in mentation and no loss of consciousness.

Amyloid angiopathy is a common cause of hemorrhagic stroke after the 5th decade of life. The hemorrhage tends to be lobar and subcortical (Image 11-4) and can be multiple. It rarely involves the deep structures (as does a hypertensive bleed). Hemorrhages may recur within months or years. Dementia occurs in 30%. Other clinical features include acute reactive hypertension, vomiting, headache, and nuchal rigidity.

Remember: There are other causes of intracranial hemorrhage, including bleeding diatheses, trauma, and bleeding into a tumor mass. Know that cocaine has been associated with development of vascular malformations and aneurysms that can be associated with major bleeding during episodes of severe, drug-induced hypertension.

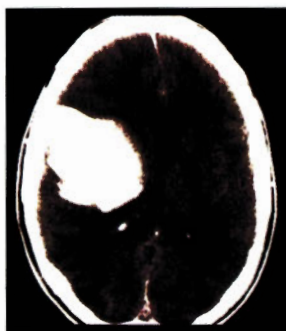


Image 11-4: CT of acute intracerebral hematoma

Treatment of Intracerebral Hemorrhage

Treatment includes the basic **supportive** care given to ischemic stroke patients. (See page 11-22.)

Any anticoagulant effects should be immediately reversed with both vitamin K and replacement of clotting factors, no matter the reasons for anticoagulation. Give protamine for any hemorrhage associated with unfractionated heparin. Also, stop any antiplatelet agents.

Control of intracranial pressure (ICP) is important, and **mannitol** is usually used.

Current guidelines to manage blood pressure recommend continuous IV antihypertensives (e.g., labetalol, esmolol, nicardipine, and enalapril) if systolic blood pressure (SBP) > 220 mmHg or mean arterial pressure (MAP) is > 150 mmHg. For those with SBP 180–220 (MAP 130–150) and increased ICP, consider intermittent or continuous antihypertensives, keeping the perfusion pressure 31–80 mmHg. Rapid reduction of BP is **contraindicated** because it can lead to vascular compromise and worsening of neurologic deficits.

Depending on the site of bleed, some clots should be surgically removed. Neurosurgeons are usually consulted.

SUBARACHNOID HEMORRHAGE

Overview

Subarachnoid hemorrhage (SAH) usually results from bleeding from an intracranial **aneurysm**. Aneurysms are most common at the bifurcation of vessels in the **circle of Willis** or its major branches. The age when this most likely occurs is between 40 and 60, and it occurs in women more often than in men.

The majority occur in the anterior circulation: 40% of aneurysms affect the internal carotid artery, 35% involve the anterior cerebral artery, and 20% the middle cerebral artery.

Subarachnoid hemorrhage can also occur after a parenchymal bleed, when there is rupture into the ventricular system. Non-aneurysmal causes of SAH are rare but include AV malformations, sickle cell disease, bleeding diatheses, pituitary apoplexy, trauma, cocaine abuse, and intracranial arterial dissection. Among persons with saccular aneurysms, there is an increased incidence of congenital polycystic kidneys, fibromuscular dysplasia of the extracranial arteries, moyamoya disease, arteriovenous malformations of the brain, and coarctation of the aorta.

Ruptures usually occur when the patient is active rather than at rest. More than 1/3 of patients report a history of “**sentinel bleed**” symptoms days or weeks earlier.

The characteristic symptoms of SAH are the acute “**thunderclap**” or “**worst headache of my life**” sensation in combination with **neck stiffness**. Common associated symptoms include loss of consciousness, nausea/

vomiting, and photophobia. Systemic manifestations of SAH may include ECG changes of large, peaked T waves, hyponatremia and diabetes insipidus.

The most important determinant of outcome is the neurological condition of the patient upon arrival at the hospital. If comatose, the prognosis is poor.

Diagnosis of SAH

Non-enhanced CT (NECT) is the best test to identify blood in the subarachnoid space. If this is negative and the NECT does not show a mass, then do a **lumbar puncture**. The CT misses **progressively more** subarachnoid bleeds as time passes from initial rupture—picking up only about 50% of bleeds after 5 days. In a SAH, CSF is bloody with xanthochromic supernatant (pink or yellow tint); however, even clear CSF does not preclude the diagnosis because it may take hours after onset of the bleed before you find red cells at the level of the spine where you draw the CSF sample.

If a bleed is still suspected in the setting of a normal NECT and LP, then angiography is the procedure of choice. CTA and MRA are alternatives to invasive angiography, and their sensitivity and specificity are close to the standard angiogram. **CTA** is now very often **included** as an enhancement to the basic triage NECT for patients with stroke symptoms. The NECT in [Image 11-5](#) shows a massive subarachnoid hemorrhage in which all the white in the brain tissue is due to blood in the subarachnoid space.

Complications of SAH

After a sentinel bleed, **rebleeding** is common. The risk is highest in the first 24 hours, but the risk remains high for at least one month.

Vasospasm may occur in up to 70% of patients and begins **3–5 days after** the hemorrhage. It reaches a peak at 5–14 days and resolves in 2–4 weeks.

The third major complication is **communicating hydrocephalus**, which occurs in 15–20% of patients after SAH. The likelihood of hydrocephalus depends on the volume of intraventricular and subarachnoid blood.

Seizures occur in 5–10%; 2/3 begin within the 1st month after the hemorrhage, while the remaining occur within the 1st year.

Treatment of SAH

If the patient is on an anti-coagulant or antiplatelet agent, stop the drug before performing any interventions. Surgical **clipping** and endovascular **coil insertion** into the bleeding vessel are the major interventions used to prevent

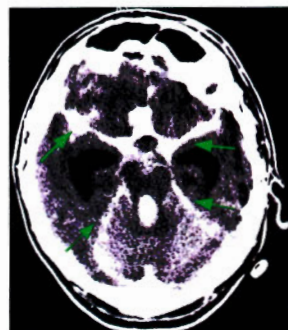


Image 11-5: Massive subarachnoid hemorrhage

the aneurysm from bleeding again. Remaining treatment focuses on preventing the complications, such as calcium blockers to prevent vasospasm. Control of ICP and blood pressure is important as well, although recommendations are less clear-cut than with intracranial hemorrhages.

Know that 1st degree relatives of patients who experienced a SAH have a 2–5x increased risk of a SAH. 2010 guidelines on the primary prevention of stroke do recommend aneurysmal screening, as discussed previously in the section on Primary Prevention of Stroke on [page 11-19](#).

Note on *other* aneurysms: **Mycotic** aneurysms are caused by septic emboli, most often from infected **heart valves**. They are usually small and occur in the distal vasculature. This is in contrast to saccular aneurysms that occur more proximally, at the branch points of the arteries (at the point where the middle cerebral artery branches off of the internal carotid artery).

SUBDURAL HEMATOMA

Subdural hematoma (**SDH**) is not always due to direct trauma; deceleration forces can also cause it. But consider SDH in patients with a history of falls, blows to the head, and vehicle accidents. Subdural bleeds are usually of **venous** origin.

SDH can be acute or chronic, and each manifests differently.

In **acute** SDH, half of the patients immediately become comatose, but the other half will remain lucid for a period of hours to days, after which cognition becomes gradually and progressively impaired until coma develops. Symptoms may also be fluctuating. Other signs of increased ICP are often present; e.g., headache, nausea/vomiting, neck stiffness, and gait abnormalities.

In **chronic** SDH, the trauma is often forgotten. Over a period of weeks, patients may develop headache, lightheadedness, slowness in thinking, apathy, drowsiness, unsteady gait, and occasionally seizure. Initially, they may be diagnosed as having a vascular lesion, brain tumor, drug intoxication, a depressive illness, or Alzheimer disease.

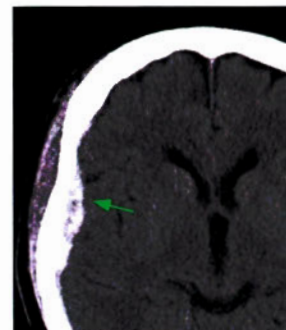


Image 11-6: Subdural hematoma

NECT is used in triage of these patients, but MRI with FLAIR is the most sensitive test. NECT in [Image 11-6](#) shows a subdural hematoma with a skull deformity.

Treatment for SDH is typically surgical—except for very small bleeds without any neurologic symptoms, which are observed closely.

Quick Quiz

- Describe the progressive workup of a patient with possible SAH.
- Which patient groups are prone to subdural hematomas?
- Describe the differences between subdural and epidural hematomas.
- A patient with history of prostate cancer and new onset of urinary incontinence should make you consider what diagnosis?

EPIDURAL HEMATOMA

Epidural hematomas, because of their **arterial** origin, evolve more rapidly than subdural hematomas. These are usually caused by temporal trauma that damages the **middle** meningeal artery—in association with temporal bone fractures. Symptoms of increased ICP are typically rapid after the head trauma, but a short period of lucidity may occur, followed by rapid obtundation.

As with SDH, diagnosis can be accomplished with NECT, but MRI with FLAIR is most sensitive.

Treatment consists of early evacuation of the hematoma via a craniotomy. If untreated, **herniation** occurs, with mortality varying from 15–40%.

TRANSIENT GLOBAL AMNESIA

Transient global amnesia (TGA) is characterized by abrupt onset of global anterograde **amnesia**, with a variable impairment of retrograde memory not associated with any other major neurologic signs or symptoms. Except for amnesia during and around the event, patients **recover completely** in 2/3 of cases within 2–12 hours, and in almost all cases within 24 hours. TGA is considered benign, and the condition recurs infrequently.

Patients are usually between 50 and 80 years of age and suddenly develop an inability to make new memories. They act disoriented, asking multiple questions repeatedly. The amnesia can even extend back to years, although more commonly just days to weeks. Some patients have accompanying nausea and dizziness. TIA can present similarly and should be considered.

Precipitating events are seen in many cases and include strenuous exercise, intense emotion, sexual intercourse, mild head trauma, pain, temperature extremes (e.g., swimming in cold water), cervical manipulation, coughing spells and other Valsalva-like activities, and medical procedures that

require anesthesia (e.g., colonoscopy). The etiology is unknown, although migraine may be a predisposing factor.

NECT and brain MRI with DWI are usually **normal**. PET and SPECT studies have shown hypoperfusion and hypometabolism in the hippocampi and associated mesial temporal lobe structures during the attack, with resolution following the attack. The attacks self-resolve. No treatment is necessary. Thiamine is often administered.

CNS METASTASES

CNS metastases typically cause a slow onset of symptoms (headaches, focal neuro deficits, impaired cognition, seizures, and/or stroke symptoms), although they can be abrupt if there is hemorrhage into a tumor.

Know the following (summarized in [Table 11-4](#)):

Parenchymal brain metastases occur most commonly with **lung, renal, and breast cancer**, as well as with **melanoma** and **lymphoma**.

Dural metastases occur with **breast** and **prostate** cancer.

Epidural metastases at the level of the spinal cord cause **back pain**, usually worse when lying down. New onset of **bladder or bowel dysfunction** (incontinence, urgency) is very important and should alert you to consider spinal epidural metastases, especially in the setting of new back pain. In a patient with a history of cancer—especially **prostate, breast, and lung** cancer—and with cord compression symptoms, metastases must be ruled out!

Meningeal malignancy is most frequent in **lymphomas**, carcinoma of the **breast**, and **melanoma**. It is less commonly seen in cancers of the lung and the gastrointestinal tract, childhood leukemia, and systemic lymphoma. MRI with contrast is the best imaging study.

Treatment of CNS metastases depend on how many metastases are present, the cancer prognosis, and the functional status of the patient. An approachable, single metastasis in a functional patient is treated with surgery and radiation. Small lesions (< 3 cm) and/or surgically inaccessible lesions can be treated with stereotactic radiosurgery. Less functional patients with numerous lesions are usually treated with whole brain **radiation** and **chemotherapy** +/- corticosteroids.

Table 11-4: Main Mets to the Brain

	Breast	Lung	Prostate	Melanoma	Lymphoma	Renal
Parenchymal	+	+		+	+	+
Dural	+		+			
Epidural	+	+	+			
Meningeal	+			+	+	

METABOLIC AND TOXIC DISORDERS

WERNICKE'S / KORSAKOFF'S

Wernicke encephalopathy and Korsakoff syndrome are considered different presentations of the same disease process. Wernicke's is milder and reversible while Korsakoff's is more severe and only partially reversible. The cause is **thiamine (B₁) deficiency**.

Wernicke encephalopathy is most often associated with alcoholism, but it can be seen in cases of protein-energy malnutrition (extreme catabolic states, kwashiorkor, marasmus), malabsorption, and specific loss of thiamine during dialysis.

It is characterized by **global confusion** with inattention, apathy, disorientation, and memory loss that worsens over days to weeks.

Abnormal eye movements are typical and include **horizontal nystagmus** and a **disordered conjugate gaze** that progresses to ophthalmoplegia (bilateral lateral rectus weakness, either in isolation or together with palsies of other extraocular muscles). The pupils may become **sluggishly** reactive to light. The person may have trouble standing or walking due to **truncal ataxia**.

Diagnosis is clinical. If the early signs of the disease are not recognized and treated, a progressive depression of consciousness occurs with stupor, coma, and death in a matter of a week or two.

Know the typical Wernicke's presentation: confused + walks drunk + trouble moving eyes.

Korsakoff syndrome is often coincident with Wernicke's and may emerge as the symptoms of Wernicke's are treated. The **amnesia** that occurs with Korsakoff's can be **both** retrograde and anterograde. Attention and mentation appear normal. Patients will often **confabulate** because of the memory problems. The stories are frequently happy-go-lucky fantasies, so-called "gleeful confabulation."

The typical Korsakoff's presentation: an **underweight, poorly nourished**, but very attentive alcoholic who tells **fantastical stories** that couldn't possibly be true and then has no memory of the discussion.

Other neurologic manifestations of the Wernicke/Korsakoff syndromes are peripheral neuropathy, retrobulbar optic neuropathy, impaired olfactory discrimination and postural hypotension.

Treatment: Immediate treatment with thiamine resolves the problem of Wernicke's and prevents Korsakoff syndrome. Once Korsakoff syndrome develops, thiamine has only partial effect. In fact, the majority of patients who emerge from Wernicke's have irreversible symptoms of Korsakoff's.

Treatment for Wernicke encephalopathy is thiamine, at a minimum dose of 500 mg (in saline) by infusion 3x/day for 2–3 days, followed by 500 mg thiamine IV

or IM daily for another 5 days. Thereafter, oral thiamine supplementation should be continued, typically at a dose of 100 mg/day. Deficiency in other vitamins and minerals, especially niacin and magnesium, should also be corrected. Wernicke's typically improves within hours of thiamine replacement.

In the Nephrology section, Book 2, we discuss how IV glucose given to a chronic alcoholic causes a decrease in the already depleted stores of phosphate and can cause hypophosphatemia. A similar sequence can occur with the thiamine stores—IV glucose can precipitate Wernicke encephalopathy in alcoholics.

LITHIUM TOXICITY

Lithium levels in the upper therapeutic range frequently cause tremor and asterixis. Remember: **Hyponatremia** causes **increased lithium resorption** from the kidney.

Above a level of 1.5 to 2 mEq/L, confusion, delirium, dizziness, nystagmus, ataxia, stammering, diffuse myoclonus, nephrogenic diabetes insipidus, vertical nystagmus, and opsoclonus are seen. Toxic lithium levels cause seizures and coma; treat with hemodialysis. The symptoms of toxicity may resemble Creutzfeldt-Jakob disease.

Note: **Opsoclonus** is uncontrolled eye movement.

ANTICHOLINERGIC TOXICITY

Classically, symptoms are:

- red as a beet (cutaneous vasodilation),
- dry as a bone (anhidrosis),
- mad as a hatter (hallucinations),
- blind as a bat (mydriasis),
- full as a flask (urinary retention), and
- hot as a hare (hyperthermia).

See the General Internal Medicine section, Book 5, for more detail on these and other toxicities and treatments.

DISEASES OF MUSCLE AND NERVE

MYELOPATHIES

Myelopathies are diseases of the spinal cord. Typical manifestations are gait ataxia, spasticity, and hyperreflexia. Bowel and bladder incontinence arise as disease worsens. There are many subcategories.

Metabolic Myelopathy

Subacute Combined Degeneration of Spinal Cord

Subacute combined degeneration of the spinal cord due to **B₁₂ deficiency** is the prototype for metabolic myelopathy. Severe B₁₂ deficiency causes segmental loss of myelin, especially in the **dorsal and lateral columns**. Clinical presentation is gradual weakness

Quick Quiz

- What is Wernicke encephalopathy? How is it treated?
- How does the presentation of the typical Wernicke patient differ from that of the typical Korsakoff patient?
- What are the symptoms of lithium toxicity?
- Describe the findings in subacute combined degeneration due to B₁₂ deficiency.
- What are risk factors for an epidural abscess? What is the most common cause?
- Describe the clinical presentations of neurosyphilis.

associated with paresthesias and loss of proprioception with development of ataxia. Severe cases end in extensive bilateral lower extremity weakness, spasticity, and urinary incontinence +/- cognitive impairment. These cognitive changes include confusion, apathy, delusions, paranoia, and mental deterioration.

Know that the neurologic changes can occur without any associated macrocytosis or anemia!

The CSF is usually normal and EMG shows slowing of sensory conduction.

Diagnose by measuring serum B₁₂, methylmalonic acid (MMA), and homocysteine (HC) levels. MMA and HC are **more sensitive** tests that are included to make a diagnosis in patients who have low-normal or normal B₁₂ levels. In states of B₁₂ deficiency, both MMA and HC are increased.

Infectious Myelopathies

AIDS

Advanced AIDS patients can get **vacuolar myelopathy** with vacuolation and deterioration of the dorsal and lateral spinal columns that presents as **ascending paresis** with a sensory component (loss of vibration and proprioception) and urinary incontinence. Clinical presentation is very similar to subacute combined degeneration of the cord. It usually accompanies HIV-associated dementia but occasionally occurs alone. Many other things can do this in a patient with virtually no immune system, but be sure to exclude a cord lesion with MRI.

Epidural Abscess

Spinal epidural abscess is a medical emergency that requires rapid diagnosis and treatment of the bacterial infection. The abscess can develop from **bacteremic seeding** from any source or **contiguous** infection after spine surgery, but rarely from lumbar puncture. Risk

factors include immunodeficiency states (e.g., diabetes, HIV/AIDS), alcoholism, and any conditions or behaviors associated with transient bacteremia (e.g., injection drug use and boils). The abscess may start as a spinal osteomyelitis and progress to an abscess, causing cord compression. **S. aureus** is the most common etiology of epidural abscess.

Remember: The main symptom of epidural abscess is back pain. Suspect epidural abscess in anyone who has been bacteremic from any cause and presents with back pain and fever. For example, rule out epidural abscess in the postpartum patient who had an epidural during delivery—the cause is almost always some type of nosocomial *Staphylococcus* species.

Initial symptoms include a few days to 2 weeks of **fever** and **backache** with localized tenderness, radicular pain, and neurologic deficits. Not all patients have all of the symptoms, and the diagnosis can be easily missed.

Abscess is best diagnosed with immediate contrasted MRI with **FLAIR** (contrasted CT is a less-sensitive alternative), TB skin test, and blood cultures. Perform myelography if the abscess is not clearly seen by MRI (or CT, if that is the only option).

Treatment: immediate decompression with laminectomy and **drainage** followed by appropriate **antibiotics**, except in cases of TB where treatment is entirely medical (using 4-drug antituberculous antimicrobials).

Tuberculosis

Pott disease is tuberculous osteomyelitis of the spine and is sometimes associated with cord compression. Usually, this form of TB is due to **reactivation** disease (rarely is it primary tuberculosis). Less than 40% have constitutional symptoms (fever, night sweats, and weight loss). They also have back pain and possible neurologic deficits and/or radicular symptoms.

Diagnosis requires a high index of suspicion and is confirmed by biopsies for pathology and culture. Supportive of the diagnosis is a positive TB skin test or serum interferon gamma release assay (IGRA).

Treatment is with standard 4-drug TB therapy. (See the Pulmonary Medicine section, Book 2, for specific details.)

Syphilis

Neurosyphilis is a potential complication if syphilis is untreated and as an earlier presentation in patients with HIV/AIDS. **Both** secondary and tertiary syphilis can affect the cord. The secondary manifestation of meningo-vascular syphilis can present as stroke or as infarction of the spinal cord (rare). **Tertiary** syphilis presents as cognitive impairment, tabes dorsalis, and/or aortitis.

The cognitive impairment can be remembered by the mnemonic **PARESIS**: **p**ersonality, **a**ffect, **r**eflexes, **e**yes (Argyll-Robertson pupil), **s**ensorium, **i**ntellect, **s**peech.

Tabes dorsalis is syphilitic involvement of the posterior columns that causes deficits in proprioception, manifesting as ataxia and paresthesias.

Tabes dorsalis is diagnosed using the following:

- Screening tests for syphilis (RPR or VDRL)
- *T. pallidum*-specific testing (MHA-TP)
- +/- Lumbar puncture and biopsies with routine path and cultures

Read more about diagnosis and treatment of syphilis (including neurosyphilis) in the Infectious Disease section, Book 1.

Inflammatory Myelopathy

Transverse Myelitis (TM)

TM is a rare problem causing inflammation of both sides of 1 or 2 segments of the cord (usually thoracic). The exact cause is uncertain, but it appears to be an autoimmune reaction. Onset typically follows a viral infection, but it is also associated with multiple sclerosis and several autoimmune disorders (lupus, mixed connective tissue disease, Sjögren's, scleroderma, and rheumatoid arthritis). There are cases of it even more rarely occurring after some vaccinations.

Clinical presentation is most often **acute** and progressive over a few days, with early paresthesias, bilateral leg weakness, and numbness with a sensory deficit below the level of the lesion. Sphincteric disturbances and backache are also common. A slight asymmetry of the symptoms and signs, a sensory level over the trunk, or a Babinski sign differentiate it from a rapidly progressive polyneuropathy such as Guillain-Barré syndrome.

MRI with contrast shows the inflammation of the cord. CSF analysis shows increased protein, lymphocytosis, and normal glucose. Treatment depends on the underlying cause (e.g., autoimmune disease vs. post-viral complication), but most patients recover some function after about 3 months. Steroids are controversial in idiopathic cases.

Compression-Induced Myelopathies

Cervical Spondylosis with Myelopathy

Cervical spondylosis (spinal osteoarthritis) with myelopathy begins with changes in the intervertebral discs. These changes occur gradually and accumulate with age. **Neck pain** is common. If the disc herniates, it will compress a nerve root, causing a **radiculopathy** at that level. Note: Radiculopathy manifests by numbness, paresthesias, weakness, and hyporeflexia in the corresponding region that is supplied by the compressed nerve root. The area affected is referred to as dermatome (sensory) or myotome (muscle groups).

When the spondylosis becomes more severe, it may compress the spinal cord itself, causing spasticity, hyperreflexia, and gait abnormalities. Gait abnormalities incorrectly may be attributed to increasing age of

the patient. A quick test is to check reflexes; a **brisk ankle reflex** in patients over 65 could be the sole clue to cervical myelopathy.

If a rheumatoid arthritis patient presents with a post-op focal neuro deficit, suspect C1–2 spinal cord trauma induced by intubation. This is likely if the patient has chronic asymptomatic C1–2 subluxation. Anesthesiologists are generally well aware of this susceptibility. Of course, other mechanisms can cause similar injury in these patients.

Thoracic Myelopathy

Thoracic sensory levels: T4 at nipple line and T10 at umbilicus. Thoracic spondylosis is distinctly **unusual**. In thoracic myelopathies, think tumor or transverse myelitis, not compression from spine arthritis.

Lumbosacral Myelopathy

The cord ends at L1–2. Lumbosacral disease affects the **cauda equina** and nerve **roots**, and may cause **L4, L5**, or **S1** radiculopathy with the following presentations:

Affected dermatomes:

- L5 = great toe (**L5** = Large toe)
- S1 = lateral side of foot by the small toe (**S1** = Side of foot near Small toe)

Affected myotomes:

- L5 = weakness of the **great toe extensor** and ankle dorsiflexion. (Patients have trouble standing on the heel and present with **foot drop**.)
- S1 = weakness of ankle plantar flexion. (Patients have trouble standing on the toes.) Ankle reflex is absent.

Lumbar spinal stenosis is a congenital narrowing of the spinal canal in the area of T10–L1, the conus medullaris. Patients are more susceptible to impingement of the cauda equina secondary to disc disease, ligamentous degeneration, and arthritis.

Lumbar spinal stenosis may result in neurogenic claudication, characterized by a deep, progressive ache in the legs, sometimes associated with lower extremity numbness, paresthesias, or weakness, which is precipitated by standing or walking for a few minutes. These symptoms are aggravated by upright posture, which extends the spine, and relieved by sitting or squatting (flexing hips/spine).

Buzz phrases that help diagnose spinal stenosis include “gets better when **bending** over the shopping cart” or “improves when walking uphill.” These activities curve the vertebral bodies and open space in the canal.

Differential diagnosis for spinal stenosis includes vascular claudication, which also causes symptoms when walking or exercising leg muscles but not when standing upright (**Table 11-5**).

Quick Quiz

- What is the clinical presentation of transverse myelitis?
- What are the symptoms of cervical myelopathy?
- What is lumbar spinal stenosis? What are the classic exacerbating and relieving body positions and movements?
- From the patient's history, what clues help you differentiate lumbar spinal stenosis from vascular claudication?
- What is the clinical presentation of syringomyelia?
- What is the clinical presentation of ALS?

Confirm the diagnosis of lumbar spinal stenosis with an MRI. Treatment is conservative (physical therapy and analgesics). Surgery is a last resort for patients who have debilitating pain not relieved with conservative measures. Surgery is indicated urgently, however, in patients with progressive neurologic deficits or incontinence.

Miscellaneous Myelopathies

Syringomyelia

Syringomyelia is a progressive myelopathy caused by **cavitation** of the **central spinal cord**, typically in the cervical region but may extend into the thoracic region. It can be idiopathic, developmental, or acquired. About 2/3 of cases are associated with **Arnold-Chiari** malformation—a congenital malformation in which there is a downward shift of the cerebellar tonsils and medulla through the foramen magnum into the cervical area of the spine, sometimes with syrinx (cyst) formation.

Syringomyelia causes a **painless weakness** and wasting of the hands and arms (brachial amyotrophy) and **segmental sensory loss** of dissociated type (i.e., loss of thermal and painful sensation with sparing of tactile, joint position, and vibratory sense). Symptoms of syringomyelia typically occur as a “suspended” or “**cape-like**” sensory deficit across the shoulders and proximal upper limbs.

The loss of pain and temperature, with initially preserved light touch and vibration sensation, indicates involvement of the crossing spinothalamic fibers in the central

part of the cord. When the anterior horn is affected, weakness and atrophy of the upper limbs occur, starting in the hands and moving proximally to include the arms and then shoulder muscles. Occipital and nuchal headaches are also very common.

Diagnose syringomyelia with MRI.

Anterior Horn Cell Disorders

Anterior horn cell problems cause **motor** deficits only. Amyotrophic lateral sclerosis (ALS), or “Lou Gehrig disease,” is the most common cause of anterior horn cell disorder. The hallmark of ALS is marked, simultaneous **upper** and **lower** motor neuron signs. Men are affected more often than women.

A patient with ALS presents with some variation of the following:

- Diffuse **hyperreflexia** and **spasticity** (upper motor neuron), along with
- **Fasciculations**, weakness, and atrophy (lower motor neuron)

Consider ALS in the patient with lower extremity weakness (possibly even falls), difficulty with fine motor skills, and fasciculations and/or atrophy on exam. Patients report severe muscle cramping. Cognitive dysfunction is **not** a feature.

ALS is relentlessly progressive, involving upper and lower extremities, truncal and bulbar musculature, and is **terminal** usually within **3–5 years** after diagnosis. Management of these patients includes determining how to proceed with respiratory and nutritional support as the disease progresses. Riluzole is commonly used, but extends life by only about 3 months.

Polio used to be the most common cause of anterior horn cell disorder; now post-polio syndrome must also be considered. Post-polio syndrome causes **areflexia** and progressive weakness **without** upper motor neuron signs. “Spinal muscular atrophy” is a set of hereditary disorders of the anterior horn lower motor neurons. A polio-like presentation today is more likely to be due to West Nile virus encephalitis.

NEUROPATHIES

Overview

Neuropathies can be divided into several categories based on which nerves are affected.

If the process involves only 1 nerve, it is called **mononeuropathy**. Mononeuropathies are generally due to **entrapment** (as with carpal tunnel syndrome); other causes include focal ischemia and trauma.

If 2 or more nerves are affected in a limited distribution, the term **mononeuritis multiplex** is used. Mononeuritis multiplex results from systemic disorders like **diabetes** or **vasculitis**.

Table 11-5: Spinal Stenosis vs. Claudication

	Change In Symptoms:		
	Walking	Standing	Sitting
Lumbar Spinal Stenosis	Worse	Worse	Better
Claudication	Worse	Better	Better

Neuropathies that symmetrically and diffusely involve the peripheral nerves are called **peripheral neuropathies** (or polyneuropathy). Peripheral neuropathies involve **distal** segments more than proximal. There are many causes of peripheral neuropathy (see below).

Involvement of multiple nerves within a plexus is referred to as plexopathy.

The workup for any neuropathy includes glucose, HbA1c level, free T₄ and TSH levels, vitamin B₁₂, ESR, creatinine, CBC, and a chest x-ray. Electromyography and nerve conduction studies (EMG/NCS) are done regardless of whether the symptoms are mono- or polyneuropathy. EMG/NCS help to identify any disease of muscle and nerve conduction. Serum protein electrophoresis, immunoglobulin electrophoresis, and quantitative immunoglobulin assays are also done if the patient is > 40 years old, particularly if the EMG/NCS suggest a demyelinating neuropathy.

Inflammatory and **hereditary** neuropathies are the most frequently missed causes of polyneuropathy. So, consider inflammatory causes and include a careful family history in your evaluation of peripheral neuropathies!

Mononeuropathies

Focal / Compressive

Focal mononeuropathies are caused by localized peripheral nerve damage, usually from a compression injury (although ischemia can also cause damage, especially in autoimmune diseases associated with vasculitis). Single nerve involvement can be caused by leprosy, sarcoid, and herpes zoster (in addition to the dermatomal rash).

The main sites of compression or entrapment are the **ulnar** nerve at the **elbow**, the **median** nerve at the **wrist**, and the **peroneal** nerve at the **knee** (discussed below). Because radiculopathies and mononeuritis multiplex can have presentations similar or identical to focal/compressive neuropathies, they must also be considered in the workup of patients presenting with focal neuropathic symptoms.

Radial neuropathy (acute wrist drop) is usually from nerve **compression** but is occasionally seen as a result of **diabetic** neuropathy (page 11-34) and may also occur

with **lead** toxicity. It has been called “Saturday night palsy” in inebriated patients because it occurs after bouts of unconsciousness whereby the nerve becomes compressed in the radial groove of the humerus. This usually resolves slowly over several weeks or months—provided the patient doesn’t continually reinjure the nerve! Physical therapy is the best treatment, using wrist splints.

Lower brachial plexus injury (from surgery/tumor/trauma) causes a claw-hand deformity, similar to that which may be seen with severe ulnar neuropathy.

Carpal tunnel syndrome (CTS) is median nerve entrapment at the wrist, usually from repetitive stress, causing sensory loss, paresthesias, and weakness involving the first 3 or 4 digits of the hand, but patients can have pain anywhere in the arm or shoulder! Thenar muscle atrophy may occur. Median nerve entrapment at the wrist almost invariably causes **nocturnal awakening** due to hand pain or paresthesias (Image 11-7). Prevalence of hypothyroidism is 1–10% in patients with CTS, so most experts recommend screening with TSH. Don’t forget about the association of CTS with acromegaly, as well.

Initial treatment of carpal tunnel syndrome is neutral alignment wrist **splints** and modifying the repetitive stress. If this is ineffective, steroid injection may help. Next step is median nerve release. Certain exercises (yoga and some specific physical therapy exercises such as “nerve gliding”) seem to help. Ultrasound helps some.

Know: Pregnancy can cause an acute presentation of CTS that typically improves after delivery. Splints are the best treatment for this patient group.

Ulnar neuropathy causes sensory loss and paresthesias in the little finger and ulnar aspect of the ring finger, as well as weakness of finger abductors and adductors. It is usually due to lesions at the **elbow** but also occurs at the entrance of the ulnar nerve to the cubital tunnel and at the **wrist**. Rarely, trauma to the heel of the hand can result in an ulnar injury. Elbow pads and splints help. Surgery is also an option for refractory cases.

Sciatic nerve compression causes pain and paresthesias that travel down the back or side of the leg into the foot or ankle. It can, like S1 radiculopathy, cause difficulty standing on toes. Unlike S1 radiculopathy, it does **not** cause a decreased ankle jerk when compared to the opposite ankle (Table 11-6).

Peroneal nerve compression usually occurs at the proximal head of the fibula, causing foot drop. Remember that L5 radiculopathy also causes foot drop.

To distinguish between peroneal nerve compression and L5 radiculopathy: Patients with peroneal nerve compression **cannot evert** the foot well but can still invert it, while L5 radiculopathy prevents or **hinders both** eversion and inversion (Table 11-7). Also, it is useful to test proximal L5 innervated muscles such as the hamstrings and thigh abductors, which will not be affected with peroneal nerve compression.



Image 11-7: Thumb muscle wasting due to carpal tunnel syndrome

Quick Quiz

- Where are the main points of compression for ulnar, median, and peroneal nerves?
- Nocturnal awakening with hand pain is frequently due to what diagnosis? What nerve does it affect?
- Mononeuritis multiplex is associated with which diseases?
- What infection should you consider in a hiker from Connecticut who presents with new onset of foot drop?
- What is the clinical presentation of Bell's palsy?

Know: Charcot-Marie-Tooth disease (page 11-35) can cause symptoms similar to peroneal nerve compression.

Mononeuritis Multiplex

Note that mononeuritis multiplex can present identically to the focal/compressive neuropathies above. Rather than being caused by nerve compression, mononeuritis multiplex is caused by a **systemic disease**. Vasculitis and vascular occlusion of the vasa nervorum (vessels that supply the nerves) are the main causes.

Consider any of the following as a possible cause of mononeuropathy +/- multiplex:

- Rheumatoid arthritis
- DM
- Connective tissue diseases
- Vasculitis
- Polyarteritis
- Lyme disease (Think of this in a hiker with new-onset foot drop.)
- Neuralgic amyotrophy (see next)

Table 11-6: S1 Radiculopathy vs. Sciatica

	Able to Tiptoe?	Decreased Ankle Jerk?
S1 Radiculopathy	No	Yes
Sciatica	No	No

Table 11-7: Radiculopathy vs. Peroneal Nerve Injury

	Foot Drop?	Able to Invert Foot?	Able to Evert Foot?
L5 Radiculopathy	Yes	No	No
Peroneal Nerve Injury	Yes	Yes	No

CNS Lyme disease is discussed in the Infectious Disease section, Book 1.

Neuralgic amyotrophy (other names: Parsonage-Turner syndrome, brachial plexus neuropathy, acute brachial radiculitis) is temporary inflammation of the brachial plexus that may follow a **vaccination** or **viral** illness. Initially, it causes extreme pain in the shoulder with radiation to the arm, neck, and back. Within hours to days after the onset of pain, the shoulder muscles and proximal arm musculature become weak. Bilateral involvement may occur. Diagnosis is clinical, supported by EMG/NCS. It improves in 1–3 years with conservative management.

Bell's Palsy

Bell's palsy is caused by dysfunction of the external 7th cranial nerve. It is regarded as idiopathic, but **herpes simplex** (or its associated immune response) is the cause of **most** cases (definitively supported by finding evidence of the virus by PCR in the affected nerve roots).

Varicella zoster is also a cause and is the probable diagnosis when a clinical scenario includes vesicles involving the tympanic membrane and external auditory canal (Ramsay Hunt syndrome).

Two important systemic diseases can also cause a facial palsy that presents identically:

- 1) Lyme disease
- 2) Acute HIV

Some experts call these palsies “Bell’s,” but others prefer to identify them as a systemic manifestation of Lyme or HIV.

Bell's palsy affects an entire half of the face, **including** the **forehead**. It causes ipsilateral facial muscle paralysis and occasionally results in no taste sensation on the anterior 2/3 of tongue, loss of lacrimation, and hyperacusis. Pregeniculate lesions are associated with the loss of taste, salivation, and lacrimation, while more distal lesions spare these functions.

To help differentiate Bell's palsy from other nerve damage, know that **cortical lesions spare** the muscles of the forehead and upper eyelid, whereas Bell's palsy affects them.

Diagnosis is clinical. Imaging of the head is reserved for patients who don't improve within 6 months or who continue to progress with facial weakness after 3 weeks.

Know that if the palsy is preceded by a period of facial twitching, the risk of tumor is higher. These patients should have urgent imaging.

Patients who begin to improve within 3 weeks will usually recover completely. If complete ipsilateral paralysis occurs, full recovery is less likely.

A week of **prednisone** shortens the course and improves function if started within 7 days of clinical onset. Studies assessing combined antiviral drugs (acyclovir or valacyclovir) + prednisone show conflicting results. Some experts give both; others do not, unless obvious signs of herpes are present; i.e., vesicles. Eyelid surgery is reserved for patients with severe palsy, or where there is corneal anesthesia or xerophthalmia not amenable to eye lubricants.

Diabetic Mononeuropathies

Know: Diabetes is associated with several cranial neuropathies. Neuropathies affecting cranial nerves 3, 4, and 6 present with eye pain, drooping eyelids, and double vision; those affecting cranial nerve 7 present with Bell's. Radial, ulnar, and peroneal isolated neuropathies are also more common in diabetics.

Note that diabetic involvement of the 3rd cranial nerve typically presents with double vision and weak eye movements without any changes in the pupils. Exam questions might have the patient presenting with **diplopia** and (pick one) chronic **sensory** dysfunction, **wrist drop**, or **foot drop**.

Polyneuropathies

Demyelinating vs. Axonal Polyneuropathies

Demyelinating polyneuropathies affect **motor** fibers and present primarily as **weakness**.

Axonal polyneuropathies are usually a **sensorimotor combination**, with sensory abnormalities appearing first (paresthesias progressing to numbness), then motor weakness appearing later.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is the most common autoimmune, inflammatory polyneuropathy. We now understand that GBS is a syndrome with **demyelinating** (most common) and **axonal** variants.

In the vast majority of cases, a mild gastrointestinal or respiratory infection precedes the polyneuropathy. GBS was reported after influenza vaccination in the late 1970s and 1990s and after the meningococcal conjugate vaccine in 2005. Causality has not been established for either vaccine, and the subject is highly controversial. There is no requirement with these vaccines to warn patients about possible GBS, but patients with a history of GBS are cautioned to avoid vaccination for the first year after their illness.

Classic **demyelinating** GBS (termed acute inflammatory demyelinating polyradiculoneuropathy [AIDP]; 90% of U.S. cases) presents as an **ascending paralysis of muscles**, including respiratory muscles, with **areflexia**. In practice, patients may have some mild sensory abnormalities and paresthesias initially, but GBS is typically portrayed as a pure motor illness with absent reflexes.

Disturbances in autonomic function and urinary retention may also be seen.

The Miller Fisher **axonal** variant (MFV, 5% of cases) is a type of GBS that includes only areflexia, ataxia, and ophthalmoplegia; e.g., patients unable to move their eyes or walk upright.

Two other rare **axonal** variants comprise the remaining 5% of cases.

Paraparetic (partial paralysis), ataxic, and purely motor or purely sensory forms of the illness have also been observed.

The CSF has a **normal** cell count and a **high protein** ("albuminocytologic dissociation"); suspect another diagnosis if the CSF has more than 10 WBC/mm³. EMG/NCS helps to characterize the variant (axonal or demyelinating).

Anti-GQ1b IgG is a unique serum protein measurable in over 80% of MFV cases of GBS, and it assists with diagnosis of this variant.

The acute axonal variants are commonly associated with preceding *Campylobacter jejuni* infections and also with development of many antibodies against the gangliosides found in peripheral nerves (especially **anti-GQ1b**).

Close respiratory monitoring and care are important. Measurement of **maximal inspiratory force** and **expiratory vital capacity** are used for the bedside estimation of diaphragmatic strength and respiratory function. The trend of these measurements is a guide to the likelihood of respiratory failure.

Plasmapheresis and IV immunoglobulin therapy (IVIG) are equally effective. Use one or the other if patients present within 4 weeks of initial symptoms.

Do **not** use steroids because they are **not** effective.

Complete recovery is the norm for about 80%; however, 10% of patients have a very prolonged course with or without significant residual weakness. Approximately 5% of patients do not survive the illness.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP begins **insidiously** and evolves **slowly**, either in a steadily progressive or stepwise manner, attaining its maximum severity after several months. In about 15% of cases, CIDP begins like a mild or moderate variant of GBS, but it slowly worsens or has a chronic relapsing course.

Chronic symmetric sensorimotor loss, EMG findings of demyelination, and elevated CSF protein define the illness.

CIDP cases are usually not traceable to an inciting event such as an infection. (Still, it's useful to think of CIDP as "Guillain-Barré that won't go away.") Consider CIDP in the patient with a demyelinating polyneuropathy (by EMG/NCS) that extends beyond 8 weeks in duration.

Quick Quiz

- Diabetes is associated with which neuropathies?
- What CSF findings are characteristic of Guillain-Barré syndrome?
- How does the treatment of CIDP differ from the treatment of Guillain-Barré syndrome?
- Name the drug used to treat diabetes that also can induce B₁₂ deficiency and cause a severe peripheral neuropathy.

LP and EMG results are identical to GBS (high protein, no pleocytosis, and demyelinating polyneuropathy). Exclude systemic disorders, specifically HIV, hepatitis viruses, Lyme, thyroid disease, diabetes, myeloma, sarcoid, and connective tissue disorders such as lupus.

Unlike in Guillain-Barré, **glucocorticoids hasten** recovery and prevent relapse in CIDP. Plasmapheresis or IVIG are also standard treatments. (Pick 1 of the 3.) Several other immunomodulators have been used chronically.

Charcot-Marie-Tooth (CMT)

CMT disease is a hereditary motor and sensory neuropathy and is by far (90%) the most common inherited peripheral polyneuropathy. There are 7 “types” composed of > 30 separate disorders under the general heading of CMT, all caused by mutations in myelin genes that are inherited variably (autosomal dominant, autosomal recessive, or X-linked).

CMT diseases are **demyelinating** and are differentiated based on genetic markers. All have both motor and sensory impairment and usually present within the first 2 decades of life. The neuropathy is symmetrical and progresses slowly. The really rare ones tend to cluster in families. Diagnosis is very simple with genetic testing. EMG/NCS is rarely needed. Treatment is supportive.

Diabetic Peripheral Neuropathy (DPN)

Diabetes mellitus is the **most common** cause of polyneuropathy in general clinical practice. DPN is an axonal **neuropathy** that mainly causes **sensory** changes, including pain, paresthesias, and **numbness**.

Muscle weakness is usually mild. Some have loss of reflexes. In long-standing cases, trophic changes are noted. Some patients have predominant loss of joint position and vibration sensations.

Control of blood sugars is the most important therapy. Effective treatments for pain include the FDA-approved DPN drugs duloxetine (Cymbalta®) and pregabalin (Lyrica®)—both are equally effective. Other drugs that are used include **tricyclic antidepressants**,

carbamazepine, gabapentin, lamotrigine, tramadol, and venlafaxine. Topical treatment with capsaicin cream and lidocaine also help.

Be aware that metformin treatment of diabetes mellitus can result in severe B₁₂ deficiency with subsequent peripheral neuropathy resembling DPN.

Alcoholic Peripheral Neuropathy

Alcohol is directly toxic to both nerves and muscles and causes many kinds of neuropathies (peripheral, autonomic, compressive). The polyneuropathy is typically axonal but is made worse if demyelination is superimposed (caused by nutritional deficiencies).

Symptoms of alcoholic axonal neuropathy start with pain and numbness in the feet in a **stocking** distribution. Over time, patients lose reflexes, proprioception, and strength.

Patients slowly recover with multivitamin therapy and abstinence from alcohol.

Remember: Acute thiamine deficiency presents as Wernicke's, a polyneuropathy (weakness of extraocular muscles and ataxia) associated with delirium.

Other Causes of Axonal Neuropathies

Other somewhat common (and Board-relevant) causes of axonal polyneuropathy include:

- Toxins, such as heavy metals (lead, arsenic)
- Chemotherapy drugs (vincristine)
- Isoniazid
- B₆ (pyridoxine) overdose from nutritional supplements
- Organophosphates
- Systemic illnesses (myeloma, porphyrias, thyroid disease, hepatitis viruses, amyloidosis, and HIV/AIDS)

Time of Onset

Differentiating among the polyneuropathies is aided by the time of onset:

- **Short** time of onset (days) is nearly always due to **inflammatory, immunologic, toxic, or vascular** etiology. Think porphyria, Guillain-Barré, and a few of the toxic polyneuropathies.
- **Long** onset (over several years) is seen with the hereditary disorders, such as Charcot-Marie-Tooth or CIDP.
- **Subacute** onset (several weeks to 2 years) occurs in the **majority**:
 - Toxicity (Lead and glue-sniffing cause mainly motor effects, while INH and vincristine cause sensorimotor effects.)
 - Nutritional deficiencies (especially B₁, B₆, and B₁₂)
 - Paraneoplastic (See Lambert-Eaton [page 11-36](#).)
 - Rheumatologic disorders

NEUROMUSCULAR JUNCTION

MYASTHENIA GRAVIS (MG)

MG is an **autoimmune** disorder. Most patients have autoantibodies to **either** the **postsynaptic acetylcholine receptor** **or** muscle-specific tyrosine kinase receptor (**MuSK**)! An even smaller group of MG patients has **neither** anti-acetylcholine receptor **nor** anti-MuSK antibodies (termed “seronegative MG”). Either or neither, but not both.

MG is associated with **thymomas** (~ 15% of patients) and **thymic** hyperplasia (~ 60%), although it is not understood exactly how the thymus is related to antibody formation.

There are 2 forms of MG:

- 1) **Generalized MG** presents as episodic weakness with repetitive movements (weakness—not tiredness, not soreness). Symptoms are worse at the end of the day. Common presenting complaints include weakness while brushing hair, putting away dishes or climbing stairs, and diplopia after a long day. Weakening with repetitive muscle stimulation during the physical exam (muscle fatigability) suggests the diagnosis. Ptosis is common. Muscles of facial expression, mastication, swallowing, and speech are affected in 80% of patients at some time in the illness. Muscle atrophy is rare, and tendon reflexes are normal.
- 2) **Ocular MG** presents as weakness localized to the eyes (lids and extraocular muscles).

Practice pearls: Demonstrating fatigable ptosis (i.e., worsening of ptosis on 30 seconds of sustained upgaze) is a good way to differentiate myasthenic ptosis from other forms of ptosis. Of course, the pupil size will be normal, unlike in Horner syndrome. In addition, the pattern of extraocular muscle weakness often does not fit the distribution of a single oculomotor nerve, and may change from one examination to the next.

Diagnosis of myasthenia gravis is best confirmed by **measuring acetylcholine receptor** and **MuSK antibodies**. Patients with generalized myasthenia usually have 1 of the 2 antibodies, whereas 50% of patients with ocular myasthenia are seronegative. More often, anti-MuSK is present in patients who are negative for anti-acetylcholine receptor antibodies. Antibody levels are not necessarily prognostic, but they do rise and fall with immunotherapy.

The edrophonium (Tensilon®) test is usually not performed because results are not as reliable as antibody measurements.

Routine electrodiagnostic studies, including repetitive nerve stimulation studies and single-fiber EMG, are useful in supporting the diagnosis.

Do thyroid function studies because **30%** of patients with myasthenia gravis have **chronic autoimmune**

thyroiditis. Look out for symptoms that suggest lupus or rheumatoid arthritis, since there is considerable overlap. Image the chest with CT or MRI in all confirmed diagnoses to rule out thymoma.

Treatments used for myasthenia gravis:

- Anticholinesterase agents (pyridostigmine [Mestinon®])
- Immunomodulators in patients **uncontrolled** on pyridostigmine (steroids, cyclosporine, mycophenolate)
- IVIG or plasmapheresis (for myasthenic **crisis** only because duration of action is very short)
- Thymectomy (takes years to see effects, but definitely perform in patients with **thymoma**)

Myasthenic crisis is a rapid deterioration of myasthenia that can cause **respiratory failure** and **quadriplegia**. A respiratory infection or certain medications can precipitate crises. Besides respiratory support, patients respond to plasmapheresis and IVIG.

Know the few drugs that can precipitate myasthenic crisis in patients with either known or undiagnosed MG:

- Aminoglycosides
- β-blockers
- Procainamide
- α interferon
- Magnesium sulfate
- Penicillamine
- Quinidine

LAMBERT-EATON SYNDROME

Lambert-Eaton myasthenic syndrome is a paraneoplastic syndrome. About 60% of cases are seen in **small cell lung cancer**; other associated cancers include prostate, breast, stomach, rectum and lymphomas. It is also seen rarely in **autoimmune** diseases. It is itself an autoimmune disease in which antibodies are produced that are specific for **calcium channels** in presynaptic peripheral nerve terminals, causing decreased release of acetylcholine from the nerve terminals.

Know the following about symptoms:

- Typical symptoms are gradually progressive proximal muscle weakness, aching thighs, dry mouth (autonomic dysfunction), and hyporeflexia, especially in the lower extremities.
- It looks like myasthenia gravis, except it **rarely** involves the **ocular** muscles and **repetitive** exercise may **improve** the weakness for the first few contractions.

Diagnose Lambert-Eaton by measuring voltage-gated calcium channel antibodies (anti-VGCC). Anti-VGCC antibodies are not 100% specific; they are sometimes found in patients who do not have Lambert-Eaton. Therefore, measure them only in patients who have a **high** pretest probability of true disease. EMG can help distinguish between Lambert-Eaton and

Quick Quiz

- What are the clinical presentations of myasthenia? How is it diagnosed?
- What other tests should be done in patients with myasthenia?
- What cancers are associated with Lambert-Eaton syndrome?
- Where is the muscle weakness that occurs with inclusion body myositis?
- Progressive limb girdle weakness in an adult patient who has a family history of the same is indicative of what diagnosis?

myasthenia—with decremental response to rapid stimulation in myasthenia and incremental response to rapid stimulation in Lambert-Eaton syndrome.

Look for malignancy in anybody diagnosed with Lambert-Eaton—especially small cell lung cancer.

Treatment includes addressing any underlying malignancy along with drugs that increase the amount of acetylcholine in the synapse (guanidine, 3,4-diaminopyridine, and pyridostigmine). Refractory cases can be treated with IVIG or prednisone.

MYOPATHIES

Myopathy simply means muscle disease. They are typically classified under neuromuscular diseases (hence their discussion here). Symptoms can be muscle weakness, stiffness, cramps, and spasms.

Inflammatory myopathies are caused by chronic muscle inflammation. Usual causes are:

- Dermatomyositis
- Polymyositis
- Inclusion body myositis

Both dermatomyositis and polymyositis usually cause:

- Elevated CK
- **Proximal** muscle weakness

Both respond to corticosteroids.

Inclusion body myositis is a **less common** type of myositis in which patients present with:

- A progressive, painless muscle weakness with involvement of proximal (initially) then distal muscles
- Elevated CK
- Oculomotor muscle sparing

Inclusion body myositis does **not** respond to corticosteroids. Muscle biopsy in inclusion body myositis shows vacuolar inclusions. More in the Rheumatology section, Book 3, on dermato- and polymyositis.

Endocrine myopathies:

Proximal muscle weakness of varying degrees may be seen in patients with hyperthyroidism, acromegaly, severe vitamin D deficiency, and conditions of steroid excess.

Hypothyroid patients have generalized muscle weakness, myalgias, slowness of contraction and relaxation, and may have increased CK. Muscle cramping is prominent in hypoparathyroidism.

Metabolic myopathies:

Consider a metabolic cause of muscle dysfunction in patients with muscle fatigue, pain, cramping, and, in more severe cases, contractures and myoglobinuria. These symptoms are precipitated by **exercise** in patients with disorders of **carbohydrate** metabolism and by **fasting** in those with disorders of **lipid** metabolism. The major categories are:

- Disorders of carbohydrate metabolism (e.g., myophosphorylase and phosphofructokinase deficiency)
- Disorders of lipid metabolism (e.g., carnitine deficiency)
- Disorders of mitochondrial function (Mitochondrial myopathies are distinguished by the presence of **ragged red fibers** on light microscopy of a muscle biopsy.)

Duchenne muscular dystrophy is an **X-linked** disorder that causes progressive muscle weakness, starting at about 2 years of age and progressing to death as a young adult. The weakness is more proximal than distal. Look for an elevated CK.

Myotonic dystrophy consists of **2 types** of inherited, adult-onset, neuromuscular disorders that have multi-system effects. Myotonic dystrophy type 1 is caused by mutations in the *DMPK* gene, while type 2 results from mutations in the *CNBP* gene. The genetic abnormalities result in weakened skeletal muscle, myotonia (prolonged contraction on muscle percussion), cardiac conduction defects, cataracts, hypogonadism, and insulin resistance. Typically, the patients will complain of skeletal muscle weakness (often **limb girdle**) and will have a positive family history. Consider this disease in a patient who presents as an **adult** with symptoms of muscle dystrophy. These patients should be referred to a neurologist who can make the diagnosis using genetic tests. Treatment is supportive only.

AIDS-related myopathy is uncommon and usually thought to be due to **zidovudine** (ZDV, AZT), but some investigators attribute this to the direct effects of the virus (controversial). Patients present with a generalized (proximal > distal) **weakness** and an **elevated CK**. Treatment is to **stop** the AZT.

NEUROMA

Morton neuroma (or Morton metatarsalgia) is a fairly common disease of the foot in which the patient has **metatarsal** pain. Generally it is diagnosed with MRI or ultrasound, which shows a small **intra**metatarsal ovoid mass. Differential diagnosis includes a metatarsal stress fracture. Treatment is surgical excision.

DEMYELINATING DISEASES

MULTIPLE SCLEROSIS

Overview

[Know **all** the following!] Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that usually begins between the ages of **20 and 30**. Women are affected more often than men (about 2:1). The incidence is higher in **northern** latitudes, possibly because of reduced sun exposure. It has recently been recognized that **vitamin D** may have an important role as a modifiable environmental risk factor. It is a chronic condition with episodes of focal disorders of the optic nerves, spinal cord, and brain, which remit and recur over a period of many years.

The disease process is thought to be autoimmune, although no specific antibodies have been found, and the disease does not predictably respond to immunomodulators. Infections as an etiology haven't been excluded from theory. One theory is that there is an initial infectious insult and an autoimmune reaction acts as a secondary trigger. Another is that MS is a result of T-cell sensitization to myelin. A familial aggregation of MS has also been reported.

The neurological symptoms depend on the region of brain that is affected.

There are 2 types of MS:

- 1) Relapsing-remitting (RLRM)
- 2) Chronic progressive

The relapsing-remitting type (normal between spells) can slowly transform into the progressive type (progresses from onset). Indeed, although 85% of cases are initially RLRM, after several years, most have transformed to the progressive type.

Clinical Manifestations of MS

Paroxysmal symptoms make up the usual course of early disease (except in chronic progressive cases). Weakness or numbness in one or more limbs is the initial symptom in about half the patients. Tingling of the extremities and tight band-like sensations around the trunk or limbs are commonly associated symptoms.

Although strict criteria are used to diagnose MS (see [page 11-39](#)), place MS in the differential anytime you encounter the following characteristic syndromes (especially if recurrent!):

- **Optic neuritis (ON)** is the most common presentation of MS eye disease and the first manifestation in about 25% of patients. It occurs at some time in 50% of all MS patients. It presents as a **rapid** loss of vision in one or both eyes, often accompanied by slight pain, especially on eye movement. The vision loss is usually **central**, but a variety of field defects may be seen. With unilateral involvement, the **Marcus-Gunn pupil**, or afferent pupillary defect, is typically seen. (Light shined into the eye **with** optic neuritis produces **less** constriction of **both** pupils than light shined into the healthy eye.) There is swelling of the optic disk, but with progression, the disk becomes pale. More than 90% of these cases recover completely.
- **Internuclear ophthalmoplegia (INO)** is another abnormal finding often seen in MS cases. INO is caused by a lesion in the "medial longitudinal fasciculus," and, although it presents as difficulty in moving the eyes horizontally, convergence is normal. (Remember that normal convergence means the patient can turn each eye inward slightly as he follows your finger to his nose, so that he continues to see a single object.) There is **adduction** paresis **ipsilateral** to the lesion, with the deficit ranging from complete medial rectus paralysis to slight slowing of an adducting saccade. Gaze-evoked horizontal jerk nystagmus is present in the abducting eye contralateral to the eye with adduction weakness. (Remember: **Adduction** means "toward the midline" and **abduction** means "away from the midline.") When you hear of a relatively young patient being diagnosed with "internuclear ophthalmoplegia," think multiple sclerosis. In older patients, however, it is more commonly due to cerebrovascular disease. The presence of bilateral internuclear ophthalmoplegia in a young adult is virtually diagnostic of MS.
- **Acute myelitis** is rapidly evolving (several hours or days) symmetrical or asymmetrical paraparesis or paraplegia, ascending paresthesia, loss of deep sensibility in the feet, a sensory level on the trunk, sphincteric dysfunction, and bilateral Babinski sign (upturning big toe with firm stroking of sole of foot).
- **Other** symptoms of MS may include generalized **fatigue**, nebulous **sensory** abnormalities (pain, paresthesias, itching, feeling of coldness or swelling, numbness [especially of the face]), **vertigo/diplopia**, lower-extremity **motor** weakness/paralysis, **ataxic** gait, and **bowel/bladder** dysfunction. Flexion of the neck may induce a tingling, electric-like feeling down the shoulders and back known as the **Lhermitte sign**.

Dementia is **not** a typical feature of MS, especially in the earlier stages, but substantial cognitive impairment may occur in some patients with **advanced chronic progressive** disease. If your patient presents with dementia and

Quick Quiz

- What are 2 ocular presentations of MS?
- What findings in CSF are helpful for the diagnosis of MS?
- What is the treatment for an acute exacerbation of MS?
- What disease is associated with the use of natalizumab?

gait abnormalities, a more likely diagnosis is Parkinson disease, progressive supranuclear palsy, or normal pressure hydrocephalus.

All symptoms of MS tend to worsen in the **heat**, called “Uhthoff phenomenon.” This is because heat increases conduction block in demyelinated pathways.

Diagnosis of MS

The diagnosis of MS is no longer based only on the history and neurologic exam. The traditional (Posner) criteria incorporated signs and symptoms indicating 2 CNS lesions separated in **time and space** and not caused by other CNS disease. CSF findings were also used. The fact that MS lesions disseminate over “time and space” has been, and still is, an essential component of making the diagnosis. MS develops slowly over time with new lesions occurring in different parts of the brain, thereby causing different neurological signs and symptoms. Newer criteria include CNS imaging.

MRI has become an essential tool in the workup of MS. T1 gadolinium MRI shows the characteristic enhancement or “plaques” of patchy myelin loss (white matter disease) with 90% sensitivity. T2 weighted MRI shows MS lesions as hyperintense areas (**Image 11-8**). Many non-MS lesions can show up as hyperintense so the **specific location** where these lesions are found has **diagnostic weight**.

The current McDonald criteria consider more heavily the **MRI findings** and have less consideration of the CSF findings than the previous (Posner) criteria. These newer criteria permit acute lesions found on MRI to be considered for the diagnosis; that is, use them to define new lesions disseminating over **time and space**:

- Time: T2 MRI showing a **new** hyperintense lesion more than 30 days after the initial event or T1 gadolinium showing **enhancement** more than 3 months after the initial event
- Space (requires 3 of the following):
 - At least 1 T1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions
 - At least 1 infratentorial lesion
 - At least 1 juxtacortical lesion
 - At least 3 periventricular lesions

In addition, consider MRI of the cord, especially if brain imaging doesn’t reveal plaques and the patient’s presentation is very suspicious for MS. The diagnostic criteria equate certain cord lesions to certain brain lesions. MRI is also essential to **rule out** conditions that could mimic MS. White matter disease due to ischemia (elderly) and vasculitis both have a very different pattern of distribution from that seen with MS.

CSF analysis is particularly useful during acute exacerbations. **IgG immunoglobulins** to **myelin** can be found in the cerebrospinal fluid.

(When these globulins are examined using electrophoresis, a **few** “bands” appear; thus the term **oligoclonal bands**.) 90% of MS patients have increased IgG index and oligoclonal IgG bands in the CSF. CSF protein and cell count is usually normal—on occasion, a small CSF lymphocytosis may be present, but should be no more than 50 cells/mm³.

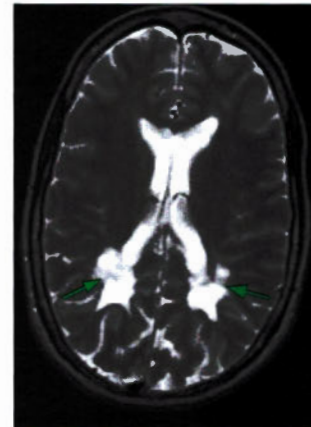


Image 11-8: Multiple sclerosis MRI

Courtesy of Steve Karsch, MD

Evoked action potentials (visual, brainstem auditory, and somatosensory evoked potentials) can help to establish the diagnosis of MS by identifying a clinically silent second lesion.

So, again, the workup for MS now includes an **MRI**, a **lumbar puncture**, and **evoked potentials**. Ultimately, the diagnosis is made using a combination of clinical history, physical exam, laboratory, and imaging data.

Treatment of MS

There is **no** cure for MS. Treatment has now become very specialized by neurologists. As a result, general internists are expected to know that the treatment of **acute** exacerbations is **high-dose corticosteroids** (as opposed to the myriad treatment options for both intermittent and progressive disease). Glucocorticoids may shorten the duration of exacerbations but do not alter the natural history of MS. Methylprednisolone, 1 gm/day for 7 days, can be followed by a rapid prednisone taper. Some cases can be treated orally. Parenteral corticosteroids are the treatment for optic neuritis.

Other drugs used to treat chronic MS are immunomodulators (beta interferons and monoclonal antibodies), antineoplastic drugs, and a synthetic amino acid polymer. Be aware of the association of progressive multifocal leukoencephalopathy (PML; discussed next) with the drug **natalizumab**, which is used to treat MS.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

PML (affects **white** matter only) is a progressive demyelination seen in patients with severe T-cell immunodeficiencies, especially HIV/AIDS patients with CD4 counts < 200 cells/mm³; it is caused by the **JC virus**. PML is also seen in patients treated with chronic steroids or monoclonal antibodies.

An example of the monoclonal antibodies is **natalizumab**, used in the treatment of MS and moderate-to-severe Crohn disease. Natalizumab is an antibody to the VLA-4 antigen expressed on activated T cells and monocytes. Most cases of PML of this type have occurred with the combination of natalizumab and other immunomodulators.

The classic presentation for PML is a **rapid** cognitive impairment associated with motor deficits, aphasia, ataxia, and visual field defects. (Manifestations are variable depending on what parts of the brain/cord are affected.) Dementia and focal cortical dysfunction such as hemiparesis, visual deficits, aphasia, dysarthria, and sensory impairment are prominent. The course is subacute and progressive, leading to death in 3–6 months.

Diagnose with brain **biopsy**. Finding JC virus by PCR in spinal fluid is supportive, although sensitivity of the PCR analysis decreases as the immune system is reconstituted on ART. ART has improved mortality in patients with PML, but many patients have persistent neurologic deficits because the nerves are unable to re-myelinate. Antiviral drugs are ineffective.

CENTRAL PONTINE MYELINOLYSIS

Central pontine myelinolysis (osmotic demyelination syndrome) occurs in patients with severe hyponatremia that is corrected too quickly with hypertonic saline. There is a progressively higher risk that is directly correlated with how long the patient had been hyponatremic before correction is started, how low the sodium concentration was, and how rapid the infusion of hypertonic saline is.

These patients may present with quadriparesis, mutism, pseudobulbar palsy, chewing and swallowing dysfunction, and/or locked-in syndrome. Paralysis is initially flaccid, but spasticity develops within a few days. See Hyponatremia in the Nephrology section, Book 2, for more discussion.

MOVEMENT DISORDERS

PARKINSONISM

[Know this topic well.] Parkinsonism (secondary Parkinson's, Parkinson syndrome) is a neurological syndrome with the characteristic set of 4 motor features (the **4 Rs**).

Signs and symptoms of parkinsonism have **4** major characteristics:

- **Resting tremor**
- **Rigidity** and flexed posture
- **Retarded movement** (bradykinesia and hypokinesia)
- Loss of postural **Reflexes**

Resting tremors at a rate of 4–5 Hz (cycles per second) occur in the distal extremities. Tremor is usually the first symptom noticed. Sometimes the tremor is present with use, with dramatic worsening at rest.

Patients with parkinsonism have diffuse **increased** muscle tone, which, combined with the tremor, causes the "**cogwheeling**" seen with passive range of motion of the limbs. The flexed posture may include the entire body. The spine, elbows, hips, and knees ultimately may become flexed. The classic hand position is flexed MCP joints with straight IP joints.

Hypokinesia/bradykinesia is the primary feature. With hypokinesia, the patient has decreased amplitude of voluntary movements—especially with repetitive tasks. This may manifest as micrographia (progressive reduction in amplitude of writing). Bradykinesia is difficulty initiating movement, slowness of movement, and decrease or loss of spontaneous movement (masked facies, tendency to sit motionless, decreased blinking).

Loss of postural reflexes causes the "festinating gait" and eventually causes falls and then the inability to stand without assistance. Festinating gait is when the patient walks progressively faster to remain under the forward center of gravity caused by truncal flexion.

There are many causes of parkinsonism. These range from Parkinson disease to drugs, toxins, metabolic disease, infections, repeated head trauma, and cerebrovascular disease.

The most common cause of parkinsonism is Parkinson disease (PD; discussed next).

Many drugs can cause secondary Parkinson's. The usual culprits are:

- Dopamine-depleting drugs (e.g., reserpine)
- Dopamine antagonists such as phenothiazines or butyrophenones
- Antiemetics such as metoclopramide

Drug-induced parkinsonism is typically much more symmetric than PD.

Common toxins: carbon monoxide and organic solvents. Repeated head trauma can also cause parkinsonism (punch drunk syndrome). Parkinsonism also occurs in some forms of Huntington disease (rigid form), frontotemporal dementia, and spinocerebellar ataxia.

Quick Quiz

- What is the cause of central pontine myelinolysis? What clinical findings are seen in this condition?
- What are the 4 motor features of parkinsonism.
- Name some common drugs used to treat Parkinson disease.
- What is a potential side effect of anticholinergic drugs when used to treat Parkinson's?
- Ropinirole is associated with what side effects?
- Selegiline can cause serotonin syndrome when combined with what other drugs?
- What is the clinical presentation of serotonin syndrome?

PARKINSON DISEASE

Diagnosis

[Know!] Parkinson disease (PD) is a clinical diagnosis. Diagnosis is especially important and often missed in the early stages.

The core features of Parkinson disease are the tetrad of:

- 1) hypo- and bradykinesia,
- 2) resting tremor,
- 3) postural instability, and
- 4) rigidity.

These are manifested as an expressionless face, poverty and slowness of voluntary movement, “resting” tremor, stooped posture, axial instability, rigidity, and festinating gait. For unknown reasons, symptoms always start on one side of the body and spread to the other side after a few years.

Rule out causes of secondary Parkinson's. Rule out other neurodegenerative disorders such as progressive supranuclear palsy (PSP; [page 11-42](#)).

The pathologic findings are loss of pigmented cells in the substantia nigra and other pigmented nuclei (locus ceruleus, dorsal motor nucleus of the vagus). Many of the remaining cells contain eosinophilic cytoplasmic inclusions, surrounded by a faint halo, called **Lewy** bodies.

The **motor** features of Parkinson disease are caused by a dropout of dopamine-producing cells in the substantia nigra of the midbrain. In a normally functioning brain, the nigrostriatal neurons produce dopamine. This dopamine is released in the basal ganglia, where it has a complex effect on the motor system, facilitating voluntary movement. When there is a decrease in dopamine from deterioration of the substantia nigra, the motor symptoms of PD emerge.

Treatment

Overview

As with MS, treatment for PD is very specialized. Focus on diagnosis, major treatments, and side effects of treatment. Staying active and **exercising** are important goals that keep patients independent as long as possible.

Drugs that **stimulate** the dopamine system are the mainstay of therapy to treat symptoms:

- **Levodopa** plus **carbidopa**, with or without the catechol-O-methyl-transferase (COMT) inhibitor entacapone (Comtan®) or tolcapone (Tasmar®)
- Non-ergot direct **dopamine** receptor **agonists**:
 - Ropinirole (Requip®)
 - Pramipexole (Mirapex®)
- Amantadine
- Anticholinergics
- Monoamine-oxidase (MAO)-B inhibitors:
 - Selegiline
 - Rasagiline

Treatment of Mild PD

Anticholinergics such as amantadine, benztropine (Cogentin®), and trihexyphenidyl are used to treat mild symptoms, especially tremor.

Anticholinergics can cause **altered mental status**, including psychosis, especially in patients > 70 years old and in individuals with cognitive impairment.

Tricyclics, which have some anticholinergic properties, may be considered in select patients for initial therapy—as long as cognition is intact.

Treatment of Mild-to-Moderate PD

Dopamine receptor agonists (ropinirole and pramipexole) can be useful as monotherapy for **mild-to-moderate** PD, but 60% of patients will require adjunctive L-dopa after 4 years.

Know that these dopa agonists, ropinirole and pramipexole, are associated with impulse control disorders, such as **hypersexuality**, **compulsive shopping**, and **pathological gambling**.

The MAO-B inhibitor **selegiline** delays the need for L-dopa in patients with mild PD by approximately 9 months. There is now some evidence that rasagiline may also slow decompensation in early Parkinson disease. To date, however, no treatment for PD has been proven to be “neuroprotective.”

Know that **combining selegiline with tricyclics or SSRIs** can potentially cause the serotonin syndrome. This problem is caused by excessive serotonergic activation of both CNS and peripheral receptors. Signs and symptoms include cognitive impairment ranging from confusions to hallucinations to coma; autonomic effects such as hyperthermia, tachycardia, shivering, and sweating; and somatic effects such as hyperreflexia

and clonus, twitching, and tremors. Symptoms can be mild to rapidly fatal, depending on the amount of overstimulation.

Treatment of Severe PD

More severe symptoms are usually treated with **L-dopa + carbidopa**. L-dopa acts as a precursor for dopamine synthesis in the basal ganglia. The carbidopa blocks conversion of L-dopa to dopamine in the periphery, a desirable effect because **peripheral** dopamine does **not** cross the blood-brain barrier. Additionally, peripheral dopamine causes side effects such as postural hypotension and nausea. Carbidopa does not help with the central side effects of L-dopa that emerge after several years. Note that L-dopa absorption may be reduced by dietary protein.

Although L-dopa is the most effective drug for PD, its use is **withheld as long as possible**, especially in younger patients, to delay the onset of complications that are common with chronic use—especially dyskinesias and motor fluctuations.

Direct **dopamine receptor agonists** (ropinirole and pramipexole) and **COMT inhibitors** (entacapone or tolcapone) are added to reduce the overall daily dose of L-dopa, to even out the serum levels of this drug, and to provide more continuous dopamine receptor stimulation.

The **older** dopamine agonists (bromocriptine, cabergoline, and pergolide) may have ergot-related adverse effects, including a risk of valvular heart disease. Cabergoline should **not** be used to treat patients with Parkinson's; it remains available for treatment of prolactinomas.

Neural tissue transplants may result in "runaway dyskinesias" and are currently **not** recommended for PD.

Complications of PD therapy include the following:

- End-of-dose "wearing off" effects (due to short half-life of L-dopa).
- Unpredictable "on-off" fluctuations that are characterized by unpredictable loss of L-dopa treatment effect and dyskinesias (50% of patients after 3–5 years).
- Psychiatric symptoms develop in **30%** of patients treated with L-dopa or dopamine receptor agonists. These symptoms include agitation, confusion, hallucinations, and delusions. Older patients with cognitive impairment are especially at risk. Approximately 17% of patients treated with a dopamine agonist develop an impulse control disorder (see above).

Know that occasionally patients who develop the psychosis with L-dopa treatment sometimes require a reduction or a switch in their meds to control their behavior. These patients are especially susceptible to development of a neuroleptic malignant-like syndrome with the switch or dose reduction. This syndrome is sometimes

termed "Parkinsonism hyperpyrexia," and presents with hyperthermia, delirium, muscular rigidity, and autonomic instability. "Drug holidays" are no longer used in Parkinson patients for this same reason.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP) is similar to Parkinson disease in that patients have bradykinesia, abnormal gait, increased muscle tone, and later develop dementia.

The disease has its onset typically in the 6th decade (range: 45–75 years of age), with some combination of difficulty in balance, abrupt falls, visual and ocular disturbances, slurred speech, dysphagia, and changes in personality. Ultimately, the characteristic syndrome of supranuclear ophthalmoplegia, pseudobulbar palsy, and axial dystonia develops. Patients usually do **not** have a tremor.

Within 2 years, the patients develop the classic symptom of a **vertical ophthalmoplegia**, typically with initial impairment of downgaze, progressing to complete ophthalmoplegia in all directions. Subsequently, the patients have trouble reading, eating, and walking down stairs. There is a gradual stiffening and extension of the neck. Within another 2–3 years, the patients may be unable to walk because of marked imbalance.

There is **no** specific treatment.

TREMORS

Overview

Tremors are divided into **static** and **action** tremors based on when the tremor occurs. Static tremors occur at rest, or when the head and extremities are fixed (termed "postural tremor").

Action tremors persist throughout voluntary movement and usually disappear at rest. Intention tremors worsen as the movement unfolds.

Exaggerated Physiologic Tremor

Usually, normal patients have an unrecognizable physiologic tremor that has a frequency of ~10 Hz. This normal tremor can be aggravated by anxiety, fright, hyperthyroidism, metabolic states such as hypoglycemia, drug withdrawal states, and certain drugs (SSRIs, corticosteroids, tricyclics, theophylline, β -agonists, nicotine, and caffeine). This tremor can be postural or seen with action.

Essential Tremor

Essential tremor is the most common type of non-physiologic tremor and is often familial. In familial cases, it seems to be transmitted as an autosomal dominant trait, with variation in age at onset and severity.

Quick Quiz

- What is a potential complication of an L-dopa dose reduction in a patient with Parkinson psychosis?
- What is the classic eye finding of progressive supranuclear palsy?
- What is the clinical presentation of essential tremor? What improves it?
- What causes tardive dyskinesia? How is TD treated?
- What is the clinical presentation of neuroleptic malignant syndrome?

It affects the hands as a postural tremor with a low frequency of **4–8 Hz**. It also can be a higher frequency and affect the head and chin as a “yes, yes” or “no, no” postural or action tremor. Essential tremor is usually benign but sometimes results in functional disability. Note that a postural tremor of the head is very unlikely to be due to Parkinson’s and is more often essential tremor. Parkinson tremors that affect the face usually involve the lips or jaw only.

The frequency of the essential tremor is typically decreased transiently by drinking alcohol, and you can often diagnose an essential tremor when patients tell you that their tremor improves after an alcoholic drink. **Propranolol** and **primidone** are effective in reducing the limb tremors. Gabapentin and topiramate reduce limb tremors a little also, but both have many side effects. In severe cases, botulinum toxin and deep-brain stimulation surgery can be tried.

TARDIVE DYSKINESIA

Tardive dyskinesia (TD) is usually a result of long-term antipsychotic drug use. The only way to be certain to avoid TD is to keep patients off chronic antipsychotics, but this cannot be accomplished in many patients with chronic psychosis.

The “atypical antipsychotics” (2nd generation drugs), such as clozapine and quetiapine fumarate (Seroquel®), may be **less likely** to cause TD. Clozapine can cause bone marrow toxicity.

Tardive dyskinesia consists of many involuntary movements including dystonia, chorea, athetosis, and tremor. The face, tongue, lips, eyelid, and bulbar muscles are most often involved, but neck, shoulder, and spine muscles with arching of the back may also be seen.

Clonazepam is a useful benzodiazepine for patients with mild tardive dyskinesias and anxiety. Some patients may benefit from the pre-synaptic dopamine depleting drug

reserpine; however, side effects of this drug may include depression, orthostatic hypotension and parkinsonism. Severe TD cases can be treated with botulinum toxin. Deep-brain stimulation surgery can be used in the most severe cases that require continued use of antipsychotic drugs.

OTHER MOVEMENT DISORDERS

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is an unusual response to antipsychotics (both “typical” and “atypical” antipsychotics), resulting in hyperthermia, rigidity, diaphoresis, autonomic instability, and altered mental status with a risk of rhabdomyolysis-induced renal failure. Occasionally, other drugs, such as metoclopramide and promethazine, can also have the same effect. Labs often show leukocytosis, electrolyte disturbances, and elevated CK levels.

This syndrome may occur days, weeks, or months after neuroleptic treatment is begun. It carries a mortality rate of 15–30% if not recognized and treated promptly. Know: Patients with **Parkinson’s** who **acutely** discontinue their dopa therapy (or reduce dose) can develop this syndrome.

Treatment of neuroleptic malignant syndrome consists of immediate discontinuation of any offending drug; use of a direct **dopamine agonist** such as bromocriptine, amantadine, or dantrolene; and supportive therapy, including adequate hydration and scrupulous pulmonary toilet. If rigidity is sufficient to affect ventilation, the patient should be sedated and paralyzed. Patients who require neuroleptics may have recurrence of neuroleptic malignant syndrome if the drugs are restarted.

Hemifacial Spasm

Hemifacial spasm is a motor analog to trigeminal neuralgia (tic douloureux). 80% of patients have a tortuous, dilated basilar artery (basilar dolichoectasia) that loops around and irritates the facial nerve! This can be caused by aneurysm or acoustic neuroma and rarely by MS.

Botulinum toxin (Botox) injections are usually effective and are the best treatments. Some patients have benefitted from surgery to separate the facial nerve from direct contact with the basilar artery. Carbamazepine, baclofen, and gabapentin have been used in treatment as well as microsurgical decompression.

Gilles de la Tourette Syndrome

Gilles de la Tourette syndrome is a movement disorder characterized by chronic (> 1 year duration) multiple motor tics and one or more vocal tics—sniffing, snorting, involuntary vocalization—and troublesome, compulsive, and aggressive impulses. Onset is

usually between 2 and 15 years of age. Many patients have comorbid attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, learning disorders, or conduct disorders.

Diagnosis is clinical and requires confirmation of both motor and vocal tics by a skilled observer.

Clonidine is recommended as first-line treatment. If the tics are severe enough to interfere with daily functioning, typical neuroleptics (e.g., fluphenazine, pimozide, haloperidol), atypical neuroleptics (e.g., risperidone, ziprasidone, olanzapine), or the partial dopamine agonist aripiprazole may be used. CNS side effects such as moodiness and depression are more common with the typical neuroleptics, while the newer atypical drugs cause more weight gain and metabolic syndrome.

Milder tics and/or associated ADHD may respond to clonidine or guanfacine. More severe ADHD can be treated with stimulants such as methylphenidate; newer data show that these drugs may not exacerbate tics as previously thought, although close monitoring is necessary. Focal tics have been treated with botulinum toxin.

Focal Dystonias

Focal or segmental dystonias are intermittent, brief, or prolonged spasms or contractions of a group of adjacent muscles that place the body part in a forced and unnatural position.

Three **focal** dystonias are commonly asked about:

- 1) Blepharospasm is bilateral, forceful involuntary eye closure and may occur as an isolated syndrome or as part of Meige syndrome.
- 2) Oromandibular dystonia is a combination of blepharospasm and oromandibular dystonia (involuntary jaw opening and jaw movements).
- 3) Spasmodic torticollis occurs when spasms of neck and shoulder muscles turn the head to one side.

A few oral drugs may offer mild relief: benzodiazepines, baclofen, anticholinergics, and sometimes antidopaminergics. However, **botulinum toxin** is now the **treatment of choice**, providing much more reliable but temporary

relief when injected directly into the affected muscles. It requires repeat injections q 2–5 months.

MISCELLANEOUS DISORDERS

ACUTE-ONSET UNILATERAL BLINDNESS

Know all of the following. See [Table 11-8](#) for a summary.

In older patients, acute onset of **unilateral** blindness is usually due to any of the following:

- Anterior ischemic optic neuropathy (AION), which may be:
 - Arteritic (secondary to giant cell arteritis)
 - Non-arteritic (less severe outcome)
- Retinal vein occlusion (secondary to diabetic retinal vascular disease)
- Retinal artery occlusion (from thrombus or emboli from the carotid artery or heart)

In the younger patient, think optic neuritis, but sometimes it can be from migraine. Migraine-induced blindness usually resolves rapidly, whereas blindness due to any of the other mentioned causes is prolonged or permanent.

Ischemic optic neuropathy, optic neuritis, and papilledema **all** can present with **swollen discs** with fundal **splinter hemorrhages**. Remember: Temporal (giant cell) arteritis also causes diplopia and jaw claudication.

“Malingering” as a cause of blindness (mono/bi) can be ruled out with evoked action potentials.

DIPLOPIA

Weak or paralyzed eye muscles cause “ophthalmoplegia” and manifest as diplopia. It can be a result of disease in the muscle itself, in the nerve that stimulates the muscle, or in the neuromuscular junction (myasthenia gravis).

Table 11-8: Causes of Acute Unilateral Blindness

Age	Disease	Etiology	Clinical Course	Exam	Outcome
Older (> 50)	Anterior ischemic optic neuropathy	< 60: atherosclerosis > 60: giant cell arteritis	Nonprogressive	Optic disk infarction	From normal to complete blindness
	Central retinal vein occlusion	Vascular disease or venous thrombosis	Nonprogressive	Hemorrhagic retinopathy	Usually some visual impairment
	Central retinal artery occlusion	Embolic or thrombotic	Nonprogressive	Cherry red spot	Only ~ 25% maintain useful vision
Younger (< 40)	Optic neuritis	Multiple sclerosis	Progressive (hours to days)	Marcus Gunn pupil; optic disc pallor	90% recover completely
	Migraine	Neurovascular	Resolves rapidly	Normal	Normal vision

Quick Quiz

- What comorbidities are associated with Tourette syndrome?
- What are causes of acute unilateral blindness in older patients?
- What do flashes followed by decreased vision suggest?
- What 4 symptoms are associated with narcolepsy?

A reminder of diseases that may present with diplopia (we have covered most of these separately):

- 3rd and 6th nerve palsies
- Myasthenia
- Graves disease
- Wernicke encephalopathy
- Miller Fisher variant of GBS
- Botulism
- Tick paralysis
- Infections/masses that affect the cavernous sinus

If you see diplopia with pain:

- Think disease in the eyeball if pain is localized **in** the eye.
- Think myopathy or orbital processes if pain is present **with movement** of the eye. Influenza is a classic cause of orbital myopathy.

Optic neuritis may also cause pain on eye movement, but it does not cause diplopia!

VISUAL FIELD DEFECTS

Scotomas

Scotomas are alterations in an isolated area of the visual field with loss or dimness of vision. Do a complete ophthalmologic exam on any patient with any type of scotoma.

Acephalic migraine (migraine without headache) can cause “fortification scotomas” that constantly change in size and may be bilateral.

Moore’s lightning streaks occur in older patients upon entering a darkened area. They are caused by the vitreous pulling on the retina; they are benign.

Retinal detachment causes flashes followed by decreased vision (from blood) or increased floaters. This is an ophthalmological emergency.

Bitemporal Hemianopsia

Bitemporal hemianopsia is the term for blindness in the lateral half of both visual fields. It has several causes:

- Pituitary adenomas (This is the one we all remember.)
- Craniopharyngioma
- Meningioma
- Aneurysm of the circle of Willis
- Sarcoidosis (rare)
- Metastatic carcinoma (rare)

COMPLEX REGIONAL PAIN SYNDROME

This syndrome causes extreme tenderness, pain, swelling, dysesthesias, and vasomotor instability in an extremity after a traumatic injury.

NARCOLEPSY

Narcolepsy is caused by a selective loss of **hypocretin** in the hypothalamus, the etiology of which is currently unknown. More than 85% of Caucasian and Japanese patients with narcolepsy-cataplexy syndrome have a specific HLA haplotype that includes HLA-DR1501 (formerly called DR15 or DR2) and HLA-DQB1-0602 (formerly DQ1 or DQ6).

Narcolepsy tetrad:

- 1) Narcolepsy
- 2) Cataplexy (3/4 of patients! With excitement, limbs become flaccid.)
- 3) Hypnagogic hallucinations (occurring as patient falls asleep)
- 4) Sleep paralysis (on waking)

Narcolepsy is treated with modafinil (a non-amphetamine drug) or stimulants such as methylphenidate or methamphetamine (many side effects and addictive potential). Cataplexy is treated with tricyclics (e.g., imipramine, clomipramine, or protriptyline) or the selective serotonin reuptake inhibitors (e.g., venlafaxine or fluoxetine).

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DERMATOLOGY

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DERMATOLOGY

Dermatology

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COMMON SKIN PROBLEMS

ATOPIC DERMATITIS

Atopic dermatitis (AD) (Image 12-1) has three age-group categories: infant (0–2 years), childhood (2–12 years), and adult (> 12 years; least common). 85% of all cases start at < 5 years of age. Each stage may be a continuation of the previous stage or may be a new finding. It is multifactorial, occasionally with increased IgE. Traditionally, there was thought to be a family history of asthma and/or rhinitis; however, recent studies have called this association into question. Patients have a decreased itching threshold and dry skin. They develop pruritic skin rashes, initially erythematous, edematous patches found on the head and neck. Extensor surfaces tend to be involved in infants; in children and adults, involvement is more often flexural. These may crust and then “weep,” at least partly from scratching.

Hydration, water-trapping agents, moderate-strength topical corticosteroids, and occasional systemic immunosuppressants are the mainstay of treatment for AD, as well as other immunosuppressants and ultraviolet radiation.

Tacrolimus (Protopic®) and **pimecrolimus** (Elidel®) are new topical immunosuppressants that are effective alternatives to topical corticosteroids. Since these don’t cause skin atrophy, they are especially good for facial lesions. There is a potential risk of cancer, so these agents are **second-line** for **intermittent** treatment of atopic dermatitis. They are not to be used on children < 2 years or anyone with a weakened immune system.

Oral cyclosporine, azathioprine, or methotrexate is used for severe AD that does not respond to conservative therapy.

Antigens, such as *S. aureus* or dust mites, and stress can exacerbate AD. Because of decreased skin defenses, AD patients tend to get chronic bacterial and fungal skin colonization and infections. Occasionally, oral antibiotics are given to decrease colonization of *S. aureus* and thus shorten the course of the disease.

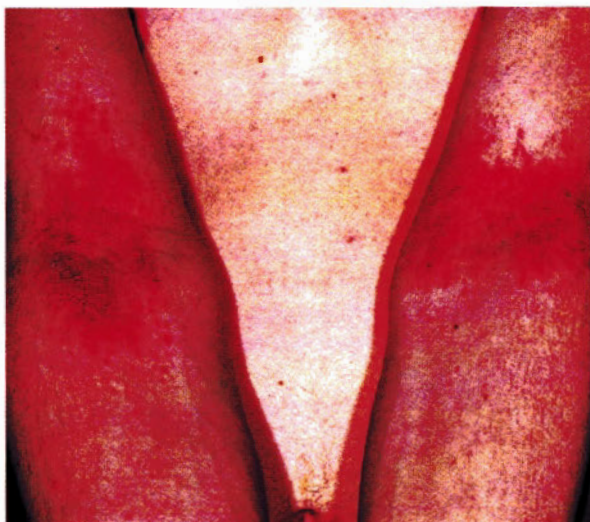


Image 12-1: Antecubital fossa with atopic dermatitis



Image 12-2: Seborrheic dermatitis

SEBORRHEA

Seborrheic dermatitis manifests as erythema and has a greasy scale (Image 12-2). It especially involves the scalp (dandruff), eyebrows, paranasal area, and external auditory canal. There is a strong association with *Malassezia furfur*, but it is unknown if this fungus is a cause or result of the dermatitis.

Seborrheic dermatitis is common in patients with HIV/AIDS and Parkinson disease.

Treatment of seborrheic dermatitis: frequent washing and an antidandruff shampoo. The active ingredients in these shampoos are selenium sulfide, zinc pyrithione, salicylic acid, or tar. The antimicrobial shampoos include ketoconazole or ciclopirox.

Use low-potency topical corticosteroids usually in combination with ketoconazole cream for skin disease.

INTERTRIGO

Intertrigo is an **irritant** dermatitis found in the macerated skin folds of obese patients. It presents with tender, brightly erythematous, moist patches in the skin folds. *Candida* can secondarily infect these areas. Suspect *Candida* when satellite papules extend beyond the main lesion.

Treat with topical antifungals and drying agents (antifungal powders, aluminum sulfate products, corn starch). Avoid the use of talcum powder in the genital area of women because of the potential for increased risk of ovarian cancer.

CONTACT DERMATITIS

Contact dermatitis can be caused by a chemical **irritant** (80% of contact dermatitis is due to irritants), or it can be of **allergic** origin (Image 12-3). The most common irritants are soapy water, rubbing alcohol, and common household cleaners. Sufficient exposure to these irritants will cause dermatitis in **every** individual. Prior sensitization is not required.

The allergic type of contact dermatitis is due to a T-cell mediated, **delayed-type hypersensitivity reaction** (Type IV hypersensitivity) in the skin. Patients must become sensitized to the antigen with one or many exposures. After sensitization and upon re-exposure, the skin will develop a pruritic lesion in 1/2 to 2 days. The most common allergens are nickel, chromium, neomycin, and oleoresin urushiol (poison oak, poison ivy, and poison sumac). First-line treatment is identifying and removing the offending allergen. Symptomatic treatment includes cool compresses, Burow's solution (aluminum acetate dissolved in water, 1:40), and topical corticosteroids. If the reaction is severe or involves the face, give systemic corticosteroids.



Image 12-3: Contact dermatitis caused by ring with nickel

ACNE

Acne Vulgaris

The clinical manifestations of acne vulgaris are:

- Open and closed comedones
- Papules
- Pustules
- Cystic lesions

Comedonal acne is noninflammatory acne, which develops in early **adolescence**. The pathogenesis involves occlusion of the follicles.

Inflammatory acne occurs as a reaction to several factors, including: *Propionibacterium acnes* within the follicle, ruptured follicular epithelium with leaking of sebum, and the immunologic response to these factors. Acne severity is genetic and hormonal, with an imbalance between estrogens and androgens. However, contrary to popular belief, most patients with acne do **not overproduce** androgens; likely the sebaceous glands are locally **hyperresponsive** to androgens (hence the genetic predisposition for many).

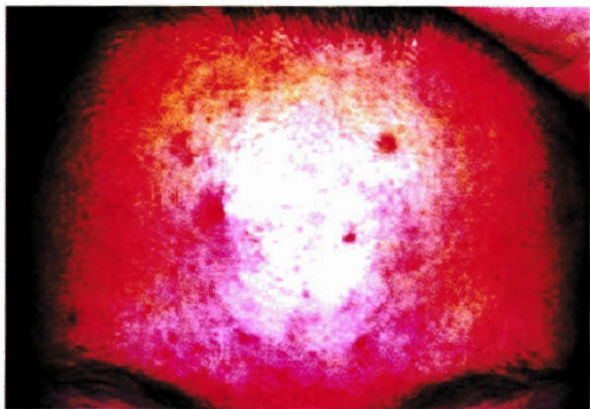


Image 12-4: Mild inflammatory acne

Factors that may exacerbate acne include cosmetics, oils, repetitive mechanical trauma (scrubbing), clothing (turtlenecks, bra straps, and sports helmets), humidity, and heavy sweating. Diet is controversial; some studies have shown an association with milk intake (exacerbating) and low-glycemic diets (ameliorating). Stress appears to worsen acne severity.

Acne vulgaris differs from rosacea by the presence of comedones (not seen in rosacea) and the lack of telangiectasia (seen in rosacea). See Image 12-4 through Image 12-6.

Note that acne is a common manifestation of increased androgens; it is often an external manifestation of polycystic ovary syndrome (PCO) in women. PCO occurs in 5–10% of women, and about 1/3 of women with acne have PCO. But having acne is not necessarily associated with increased androgens.

Treatment of Acne Vulgaris

Comedonal (noninflammatory) acne: **Topical retinoids** are drugs of choice for **comedonal** acne. These include adapalene, tretinoin, and tazarotene. (Note: Tazarotene [Tazorac®, Avage®] is contraindicated in pregnancy!)

Side effects are mainly skin irritation and photosensitivity. Other agents for comedonal acne include topical salicylic acid, azelaic acid, and glycolic acid; all 3 have antimcomedonal activity.

Mild inflammatory acne (Image 12-4): **Benzoyl peroxide** in combination with topical **erythromycin or clindamycin** is used to treat the *P. acnes* of inflammatory acne. The combination therapy decreases development of resistance, and commercial preparations are available that have both products. Topical retinoids are also useful in combination. Topical dapsone, an effective antimicrobial agent, was initially approved by the FDA in 1995; in 2009, it was remarketed with the trade name Aczone®.

Moderate-to-severe inflammatory acne (Image 12-5): This usually requires **oral antibiotics** in addition to the above topical therapy. Oral antibiotics used are tetracycline, doxycycline, minocycline, and erythromycin. TMP/SMX and amoxicillin are tried in resistant cases.

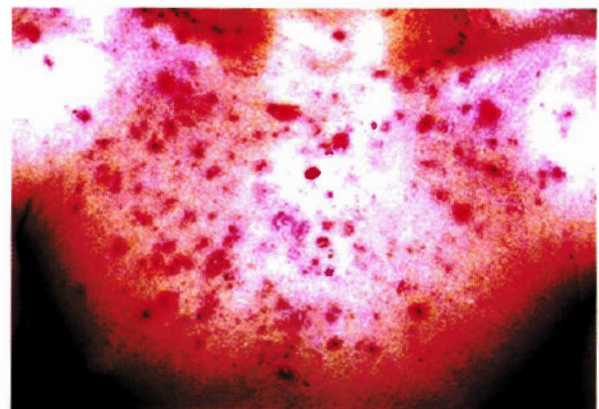


Image 12-5: Moderate-to-severe inflammatory acne

Quick Quiz

- What is the clinical presentation of seborrhea?
- What is the clinical presentation of intertrigo?
- Contact dermatitis is an example of what type of hypersensitivity reaction?
- What are the serious side effects of isotretinoin?
- How can you tell the difference between rosacea and acne vulgaris?
- What finding on the buccal mucosa can be seen with measles? Describe and name the finding.

Isotretinoin (Amnesteem®, Claravis®, Sotret®; 1.0 mg/kg/d) is highly effective in severe nodulocystic, scarring, or resistant cases but is also a powerful **teratogen**. The use of isotretinoin is restricted to physicians who have registered with the electronic FDA system (called the “iPLEDGE program”) and requires multiple steps in order to prescribe (e.g., 2 pregnancy tests, 2 forms of birth control). Serious side effects include pseudotumor cerebri (especially if used with **tetracyclines**), depression and psychosis, pancreatitis, marked hypertriglyceridemia, hearing loss, night vision loss, and skeletal abnormalities.

If oral isotretinoin is used, all other acne treatments must be stopped. Notably, concurrent use of oral isotretinoin and the family of tetracycline antibiotics can cause pseudotumor cerebri.

Hormonal therapy with oral contraceptives is effective for women with excessive androgen production, particularly PCO. Spironolactone, which has anti-androgen effects, is also used as hormonal therapy.

Acne Rosacea

Acne rosacea (Image 12-6) occurs in mostly middle-aged patients and presents with erythema, **telangiectasias**, and acne-like lesions on the central face. Even before the lesions, the patients may have a **flushing reaction** to



Image 12-6: Acne rosacea

various stimuli (e.g., alcohol, stress). Once the rosacea manifests, the flush may become **permanent**. Treatment is usually topical **metronidazole**, azelaic acid, sulfur/sulfacetamide preparations, and tetracycline antibiotics. Rhinophyma (bulbous nose) can occur, particularly in older men, and may require surgical therapy. Of note, rosacea does not have comedones, unlike acne vulgaris. Rosacea has an association with bacterial overgrowth syndrome in the gut.

HIDRADENITIS

Hidradenitis suppurativa (acne inversa) is a chronic inflammatory scarring process involving apocrine gland-bearing areas, usually the **axillae** and the **groin/perianal** region (Image 12-7). This disease occurs in both sexes (w > m, 4:1)—women tend to have more axillary and vulvar involvement while perianal involvement is more common in men.

The disease process begins with dilated, occluded follicles (comedones) that often have multiple openings. Subsequently, the disease can range from mild to severe (induration, scarring, pitting, and draining abscesses).

Treatment for hidradenitis is often **ineffective**. If applicable, weight loss should be recommended. Avoid deodorants (antiperspirants okay); tight, synthetic clothing; and prolonged exposure to hot, humid environments. Even if fluctuant, the lesions may be sterile. Intralesional steroids may work in these instances. However, treat acute infections with incision, drainage, and packing. Try tetracycline or erythromycin, then a topical antibiotic for prophylaxis. Oral contraceptives may be used in women. Give zinc gluconate to prevent lesions. Newer immunomodulating drugs have been used with some success; e.g., TNF- α inhibitors. Surgical excision is the only definitive therapy for severe cases.

MOUTH FINDINGS

Know all of these!

Hyperpigmented gingiva is seen in **Addison** disease.

Koplik spots (Image 12-8) are small white papules on an erythematous base, which are found on the buccal mucosa in patients with **measles**. These usually precede the skin lesions by several days.

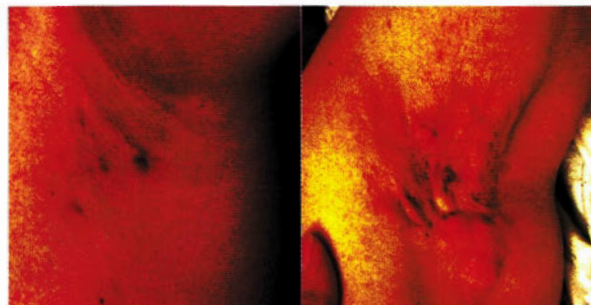


Image 12-7: Hidradenitis suppurativa; mild vs. severe



Image 12-8: Koplik spots



Image 12-9: Oral hairy leukoplakia

Oral hairy leukoplakia (Image 12-9) most commonly occurs in patients with HIV/AIDS. It appears as areas of ribbed whiteness along the sides of the tongue. This is due to Epstein-Barr virus in the superficial layers of the tongue's squamous epithelium.

Peutz-Jeghers syndrome (multiple intestinal hamartomatous polyps) should be ruled out in patients with melanotic pigmentation (**lentigines**) on the lips and buccal mucosa.

Beefy red tongue is seen in **pernicious anemia** and various B vitamin deficiencies. It also can be associated with **glucagonomas**—discussed under Skin Cancer and Skin Findings on page 12-12.

Macroglossia (big tongue) is associated with multiple myeloma, primary amyloidosis, lymphoma, hemangioma, acromegaly, and Down syndrome.

White lesions: candidiasis, hairy leukoplakia (AIDS), lichen planus. Lichen planus also causes ulceration and lace-like patches.

“Geographic” tongue has the appearance of migratory denuded red patches. It is asymptomatic and benign (Image 12-10). It is often associated with psoriasis.

“Strawberry” tongue is associated with scarlet fever, toxic shock syndrome, and Kawasaki disease (mucocutaneous lymph node syndrome; children usually).

“Bald” tongue is an atrophy of the tongue associated with pellagra, iron deficiency anemia, pernicious anemia, and xerostomia (salivary gland problems as seen in Sjögren syndrome, lymphoma, mumps, and sarcoidosis; occasionally idiopathic).

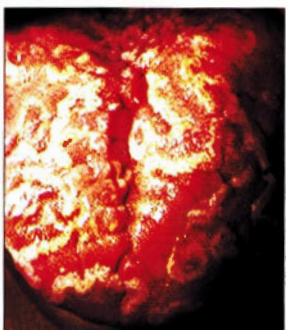


Image 12-10: Geographic tongue

CUTANEOUS DRUG REACTIONS

The following are the most frequent drug-associated skin changes. Know all of them.

Penicillin (PCN):

- **Immediate** hypersensitivity reaction; anaphylaxis (IgE)
- **Delayed** hypersensitivity reaction; immune complex reaction, such as vasculitis or morbilliform eruption

Tetracyclines: photosensitivity (demeclocycline > doxycycline > tetracycline > minocycline).

NSAIDs: urticaria/angioedema in 1%, asthma in 0.5%, and may cause photosensitivity or toxic epidermal necrolysis (TEN).

Phenytoin:

- Hypersensitivity syndrome: rash, facial edema, lymphadenopathy, and hepatitis
- Various skin reactions, including erythema multiforme
- Hypertrophied gums

Corticosteroids: skin changes, including striae, atrophy, telangiectasia, pigmentary changes, and acne-like lesions.

Warfarin: necrotic patches (**necrosis**) of skin appearing 3–10 days after starting warfarin.

Radiocontrast dye: This can cause urticaria/erythema (1/15), and anaphylaxis (1/1,000). There is a 30% repeat reaction incidence in someone with a previous reaction to contrast dye. The repeat reaction can be very serious. Prophylaxis with diphenhydramine and corticosteroids (start 1–2 days prior) will decrease this reaction 10-fold.

ACE inhibitors: **Angioedema** occurs in only 0.5% of patients treated with an ACE inhibitor. However, because such a large number of patients receive this drug, it is one of the most common causes of isolated angioedema. Angioedema can occur at any time during therapy with ACE inhibitors.

INFLAMMATORY SKIN DISORDERS

NOTE

Many of the disorders described here are presented in more detail in the Rheumatology section, Book 3.

PSORIASIS

Overview

Psoriasis is a response triggered by T lymphocytes in the skin. The epidermis becomes hyperproliferative, producing more skin at a faster rate than normal.

Quick Quiz

- What viral infection causes hairy leukoplakia?
- A beefy red tongue is seen with which underlying disease states? Macroglossia?
- What adverse cutaneous reactions are associated with phenytoin?
- Nail pitting with onycholysis is a fairly specific finding for what dermatologic disorder?
- Which drugs should be added to the regimen for patients with psoriatic arthritis?

Types of Psoriasis

Plaque psoriasis is the most common type (Image 12-11). It presents in young adults with well-defined, stable, slow-growing, **non-pruritic**, erythematous skin lesions with distinctive **mica-like** (silvery) scales. It is usually symmetric and occurs on extensor surfaces of the knees and elbows, the sacral area, and the scalp. Koebner phenomenon (outbreak in the area of trauma) is common. See the Rheumatology section, Book 3, for psoriatic arthritis.

Guttate (eruptive) psoriasis is an abrupt eruption of multiple small lesions, which usually occurs on the trunk of children or young adults with no previous history of psoriasis. There is a strong association with upper respiratory infections and group A beta-hemolytic strep.

Flexural (inverse) psoriasis affects skinfold areas. Called inverse because it is not on the extensor surfaces.

There are 2 especially **severe** types of psoriasis:

- 1) Erythrodermic psoriasis
- 2) Pustular psoriasis

Erythrodermic psoriasis is an exfoliative reaction in which the entire surface of the skin becomes red, warm, and scaly; and the patient is unable to control body temperature (hypo/hyperthermia is common). Dehydration, hypoalbuminemia, and anemia of chronic disease are common sequelae.

All types of psoriasis, including erythrodermic psoriasis, can be precipitated/exacerbated by sunburn, infection (virus, strep pharyngitis), heavy alcohol intake, and drugs (especially antimalarials, lithium, and **beta-blockers**).



Image 12-11: Plaque psoriasis

Pustular psoriasis has many small pustules, often coalescing to form “**psoriatic lakes of pus**.” There are 2 forms:

- 1) The **localized** form affects only the palms and soles. It is associated with DIP joint arthritis.
- 2) The rare, **generalized** form (von Zumbusch type) is the **most severe form** of psoriasis and may occur with the erythrodermic type.

Nail Changes

The most specific nail finding is an “oil spot” on the nails. “Ice-pick” **pitting** of the nails is also common. These pits will usually be in small groups on the nail. **Thickened** nails and **onycholysis** (separation of distal nail from the nail bed) are also common in psoriasis (Image 12-12). Having pitted nails in association with onycholysis is fairly specific for psoriasis and psoriatic arthritis.



Image 12-12: Pitted nail with onycholysis

Drugs Used to Treat Psoriasis

(Know all of these.)

Topical corticosteroids: Plaques are usually treated with topical corticosteroids. Long-term use of high-potency steroids may cause thinning of the skin, striae, and steroid-induced rosacea on the face. **Oral** corticosteroids may actually **worsen** the disease by causing a “rebound flare.”

Tar is a time-honored treatment and is often still used in a compounded preparation with a corticosteroid. Tar preparations stain clothes but are well tolerated.

Calcineurin inhibitors: **topical tacrolimus** (Protopic®) and **topical pimecrolimus** (Elidel®). These are often used for facial and intertriginous areas when high-potency steroids should be avoided. Be aware of the FDA-boxed warning for a potential increased risk of lymphoma and skin malignancy.

Retinoids (vitamin A derivatives):

- Tazarotene gel (Tazorac®, Avage®) will decrease the hyperkeratosis or thick scales associated with psoriasis.
- Acitretin (Soriatane®), a second-generation oral retinoid, is used for the severe forms of all types

Do **not** use either drug in women with child-bearing potential.

Vitamin D₃ analog:

- Calcipotriene (Dovonex[®], a synthetic vitamin D₃ analog) compares well with topical steroids but without the risk of thin skin or striae.
- Calcitriol (Vectical[®], a synthetic vitamin D₃ analog in an ointment base).

Immunosuppressants:

- Methotrexate
- Cyclosporine
- Azathioprine

Biologic immunomodulators:

These are **newer, effective** treatments for psoriasis:

- T-cell memory effector inhibitor: **alefacept** (Amevive[®])
- TNF-alpha inhibitors: **etanercept** (Enbrel[®]), **infliximab** (Remicade[®]), **adalimumab** (Humira[®])
- IL-12 and IL-23 blocker: **ustekinumab** (Stelara[®])

Ultraviolet light may be added to the above treatments. UVB (290–320 nm) therapy is often used. Narrow-band UVB (311 nm) is possibly more effective than the broader spectrum treatment (few good studies) but requires more expensive equipment.

“PUVA” (oral **psoralen** + UVA light [320–400 nm]) is also very effective and is usually given to those who fail UVB. UVA penetrates more deeply than UVB and is less likely to burn (hence, the photosensitizing psoralen), **but** it is associated with increased likelihood of skin cancer, including melanoma.

Any patient with psoriatic arthritis is at risk for permanent joint damage and should be treated with a disease-modifying oral/injectable agent (cyclosporine, methotrexate, or the biologics).

Methotrexate and **cyclosporine** are commonly used for **widespread psoriasis**, especially with **arthritis**. Remember: Do **not** give methotrexate to patients with liver/renal disease or a history of alcohol abuse.

Treatment of Psoriasis

Mild plaque psoriasis: Treat with hydration and water trapping agents. Use high-potency or ultra-high-potency topical corticosteroids for mild plaques everywhere except more sensitive areas.

For the face, axillae, and genitalia, use:

- low-potency corticosteroids,
- topical tacrolimus or pimecrolimus,
- calcipotriene, or
- topical retinoids (tazarotene).

Moderate psoriasis: Treat with high-potency topical corticosteroids, calcipotriene, topical retinoids (tazarotene), or UVB therapy. Depending on

morbidly associated with the disease, consider treatment with methotrexate, acitretin (Soriatane[®]), or a biologic.

Widespread or severe: Treat with methotrexate, cyclosporine, or a biologic. A combination of UVB or PUVA with acitretin can also be used.

Guttate psoriasis: Treat with UVB +/- topical steroids. Treat any streptococcal infection for at least one month.

Flexural psoriasis: Treat with low-potency topical corticosteroids or topical tacrolimus/pimecrolimus.

LUPUS**Systemic lupus erythematosus (SLE):**

Malar (or butterfly) rash occurs in about half of SLE patients. Classically, this rash involves both cheeks and extends across the bridge of the nose, sparing the nasolabial fold. The malar rash is erythematous and either flat or slightly edematous and often occurs after sunlight exposure (**photosensitive**). No scarring.

Patients can get a red, scaly rash on the backs of the hands, usually **between the joint spaces** of the fingers (as opposed to dermatomyositis, where the rash is over the knuckles and spares the spaces between).

Patchy and diffuse nonscarring alopecia is common.

More on SLE in the Rheumatology section, Book 3.

Discoid lupus erythematosus (DLE): **Discoid** lesions are erythematous and raised with tightly adherent scales. They cause atrophic **scarring**. They usually occur on sun-exposed areas, including: the face, scalp, neck, and ear canals. Only 5–10% of DLE patients develop SLE.

SCLERODERMA

- Localized = morphea (affects skin only)
- Systemic = progressive systemic sclerosis (diffuse form) or CREST syndrome (limited form)

Morphea is a localized scleroderma on the skin characterized by plaques that become sclerotic with a hypopigmented center and erythematous border. It usually occurs in children or young adults. It can be just a few lesions (localized morphea) or widespread with some confluence (generalized morphea).

Progressive systemic sclerosis (Image 12-13) usually starts with recurrent, nonpitting edema of the face and distal extremities and involves internal organs. Sclerosis of the skin begins at the distal digits and moves proximally. Patients may develop tight, unwrinkled skin over the face, and the

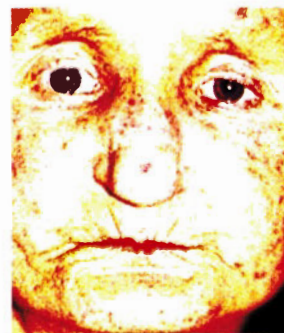


Image 12-13: Systemic sclerosis

Quick Quiz

- Characterize the malar rash of systemic lupus.
- What are the manifestations of limited systemic sclerosis?
- What skin findings are associated with sarcoidosis?
- What are the skin manifestations of dermatomyositis?

fingers may become tight and sausage-shaped. **No** nail changes, but nailfold capillary changes are commonly seen and correlate with severity of disease. **No** satisfactory treatment.

Limited systemic sclerosis (previously **CREST**) is a grouping of symptoms that has limited systemic involvement. These patients present with **calcinosis** cutis (small tender nodules on the fingers), **Raynaud** syndrome, **esophageal** dysmotility, **sclerodactyly** of the fingers, and **telangiectasias**.

SARCOIDOSIS

Sarcoidosis is an immune-related **noncaseating** granulomatous disease that often affects the lungs, lymph nodes, eyes, and **skin**. Skin involvement is seen in about 20% of cases. Lesions are:

- Erythema nodosum (see next). Sarcoidosis is one of the most common causes of E. nodosum. Unlike the other skin findings, this is associated with a **good** prognosis and shows no caseation. Do **not** biopsy E. nodosum in sarcoidosis for diagnosis—the histopathology will just show a panniculitis (inflammation of the fat) and not granulomas.
- Erythematous papules, mainly around face.
- Scar sarcoidosis presenting as granulomatous changes in a healing skin wound (e.g., laceration, tattoo).
- Plaque-like lesions.

Sarcoidosis is the second-greatest mimic of other diseases (first is syphilis); it can mimic many dermatologic diseases.

Lupus pernio is a type of sarcoidosis that has skin changes ranging from violaceous lesions on the tip of the **nose** and **earlobes** to large purple nodules/tumors on the **face** and **fingers**. It has a slow onset and almost **never** resolves!



Image 12-14: Erythema nodosum

The best prognosis of the sarcoid skin changes is with E. nodosum or the small papules. Treat cutaneous sarcoid with intralesional topical steroids, occasionally antimalarials, and methotrexate.

ERYTHEMA NODOSUM

Erythema nodosum (**Image 12-14**) consists of red, warm, very tender nodules that usually appear on the shins. Causes of erythema nodosum:

- **Sarcoidosis** (common)
- Inflammatory bowel disease
- Infection (**TB**, streptococcal, deep fungal)
- Drugs (especially **oral contraceptives**, sulfas, and penicillins)

Worldwide, streptococcal infection is likely the most common cause of erythema nodosum. Know all of these causes!

DERMATOMYOSITIS

Buzzwords: periorbital **heliotropic** rash (+/- periorbital edema) (**Image 12-15**). This is a violaceous (purple), sometimes scaly rash around the eyes.

Patients can also get photodistributed, erythematous, scaly plaques—similar to psoriasis.

Gotttron papules are flat-topped, reddish-to-violet, sometimes scaling papules; sometimes, they just look like “cigarette paper” crinkling of the skin over the **knuckles** (MCP, PIP, and/or DIP). Gotttron papules are the most **specific** finding with dermatomyositis. They may be described only as a “rash” or “eruption” over the knuckles (**Image 12-16**). Again, this contrasts to the finger rash in systemic lupus erythematosus that occurs between the knuckles.

Usually patients will have symmetric proximal muscle weakness.

Treatment is **corticosteroids**. This is typically given for one year in a slowly tapering dose. A steroid sparing drug (azathioprine or methotrexate) is sometimes started with initial treatment; other clinicians start it when there is failure to respond to prednisone.

Antimalarials (hydroxychloroquine) help with the skin disease but do nothing for the muscle disease.



Image 12-15: Periorbital heliotropic rash

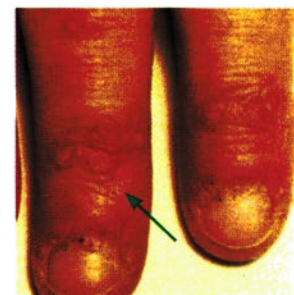


Image 12-16: Gotttron papules



Image 12-17: Keroderma blennorrhagicum



Image 12-18: Pyoderma gangrenosum

Courtesy of Kimberly Salley, MD

TNF-alpha inhibitors and leflunomide (immunomodulators) also are useful for refractory disease. Remember: In older patients, dermatomyositis may be a **paraneoplastic** phenomenon. (GU/ovarian, GI, and respiratory are most common.)

REACTIVE ARTHRITIS

Reactive arthritis (previously Reiter syndrome) causes pustular scaly lesions on the palms and soles (**keroderma blennorrhagicum**; Image 12-17) and **circinate balanitis** on the penis. Patients will also have dysuria, conjunctivitis/uveitis, and arthritis.

VASCULITIS

Vasculitis presents as **palpable purpura**, usually starting on the legs. There are many causes of vasculitis, including: infection (viral, bacterial, etc.), collagen vascular disease, and inflammatory bowel disease. Up to 50% of self-limited cutaneous cases may be idiopathic. If a patient presents with arthralgias, abdominal pain, and palpable purpura, think Henoch-Schönlein purpura.

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is an inflammatory ulcer usually occurring on the legs (Image 12-18). It is often associated with inflammatory bowel disease. It can also occur with rheumatoid arthritis, leukemia, IgA gammopathy, and chronic active hepatitis. Although a skin biopsy is **not** diagnostic, it serves to exclude other causes for ulceration. The classic presentation is a deep ulceration with an inflamed border that overhangs the ulcer. Treating the colonized bacteria usually does not help. First-line treatment is prednisone.

SWEET SYNDROME

Sweet syndrome is an inflammatory disorder sometimes associated with leukemia; it is also called acute febrile neutrophilic dermatosis. Patients have **high fever** and painful red plaques, ~ 1 inch in diameter. A skin biopsy shows

a dense, but benign neutrophilic infiltrate. 10% or less are associated with leukemia. (AML and myelomonocytic leukemia are the most common.) Corticosteroids are usually quickly effective.

VITAMIN DEFICIENCIES

Deficiency of B₁₂, folate, or niacin may cause diffuse hyperpigmentation, as well as hair and nail changes.

Niacin deficiency results in the 3 Ds: dermatitis, diarrhea, and dementia.

Zinc deficiency causes an irritant eczematoid red rash that usually involves the nasolabial folds, extensor surfaces, and perineum/scrotum.

SKIN INFECTIONS

BACTERIAL SKIN INFECTIONS

Much of the following and all treatments are covered more fully in the Infectious Disease section, Book 1.

Corynebacterium

Erythrasma is a well-defined, red lesion with some slight scaling. It is usually found in the axilla, groin, and toe webs. In obese women, it is seen under the breasts. Gram-positive *Corynebacterium minutissimum* is frequently isolated from the lesion (especially after it has become scaly or macerated). DDx: fungal infection and intertrigo (an irritant dermatitis found in the skin folds of obese patients). Diagnosis: Erythrasma fluoresces **bright red** with the Woods lamp. Treat with oral or topical erythromycin +/- an "-azole" antifungal cream.

Staphylococcus aureus

Impetigo. *S. aureus* is by far the most common cause of impetigo, which starts as an erythematous, vesicular lesion that quickly becomes pustular and crusty ("honey-colored crust"). Methicillin-resistant *Staphylococcus aureus* (MRSA) is the cause of many **community outbreaks** of impetigo. Treatment is covered in the Infectious Disease section, Book 1.

Bullous impetigo usually occurs in young children < 2 years old and presents with the acute onset of large, loose bullae (Image 12-19). An exotoxin/exfoliotoxin causes cleavage of the epidermis.

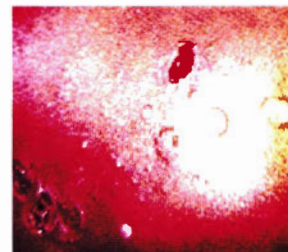


Image 12-19: Bullous impetigo

Courtesy of CLM

Quick Quiz

- Pyoderma gangrenosum is associated with what systemic illness?
- How does zinc deficiency manifest on the skin?
- What 2 organisms can cause impetigo?
- How does SSSS differ from toxic epidermal necrolysis?
- Characterize the lesions of disseminated gonorrhea.
- What is the significance of finding a lesion of ecthyma gangrenosum on physical exam?

Staphylococcal scalded skin syndrome (SSSS).

Patients with SSSS present with tender, red, peeling skin—due to circulating toxins from localized staph infection or colonization, usually occurring at a non-skin site (sinuses; umbilicus in infants). Skin changes are similar to those seen in toxic epidermal necrolysis (noninfectious; rather, a side effect of drugs), so consider it during the workup. The skin in SSSS separates much **more superficially** than in toxic epidermal necrolysis. The peeling skin is caused by a similar exotoxin/exfoliotoxin as seen in bullous impetigo; however, it circulates systemically in SSSS.

Toxic shock syndrome (TSS). *S. aureus* and *S. pyogenes* are the causes of TSS. TSS presents with abrupt development of **hypotension** and **multiorgan** system failure. Patients have a diffuse scarlatiniform rash followed by desquamation of the palms and soles.

Folliculitis (inflammation of the follicle) and **furuncles** (deep folliculitis or “boil”) are usually caused by *S. aureus*. Be aware that folliculitis associated with hot tub use is often caused by *Pseudomonas*, **not** staph.

Streptococcus pyogenes (group A strep)

Impetigo. Group A strep is a cause of impetigo—a skin infection confined to the epidermis. Also see *S. aureus*, above. **Ecthyma** starts as an impetigo and then becomes deeper, causing shallow ulcerations.

Erysipelas is an explosive superficial infection (often caused by group A strep), confined to the dermis, that spreads quickly through skin lymphatics (Image 12-20). There is a **clearly demarcated** area of redness that is often palpable, indicating infection. It usually starts from a superficial



Image 12-20: Erysipelas

abrasion, typically around the central face, with erythema and swelling. **Lymphangitic spread** with red streaking is seen.

Necrotizing fasciitis is a deep, soft tissue infection involving subcutaneous fat and fascia. Unlike erysipelas, it does not have a distinct border and can be difficult to diagnose early. The infection is often polymicrobial (e.g., group A strep + anaerobes). There is high mortality even with appropriate medical and surgical intervention.

Scarlet fever causes “**scarlatina**”—a fine, red, sandpaper-like rash with desquamation of the skin, commonly occurring during healing. “**Strawberry tongue**” commonly presents in the acute phase.

Streptococcal toxic shock syndrome (TSS) causes symptoms similar to staphylococcal TSS (described above). Treatment is with IV penicillin (PCN) + clindamycin +/- IVIG.

Strep throat. **PCN** is far and away the best treatment for a known group A strep throat infection. Give oral PCN (x 10 days) or IM benzathine PCN. **Erythromycin** for PCN-allergic. **Clindamycin** is often added to PCN when there is serious infection, such as necrotizing fasciitis or toxic shock.

Gonococcus

Disseminated gonococcal **infection** causes a few (usually < 12) acral hemorrhagic lesions, which become pustular, often around the joints. Culture of disseminated exudate is usually **negative**. Culture is more sensitive when taken from the site of infection (cervix or urethra).

Meningococccemic skin signs start as macular or petechial lesions and evolve to large purpura.

Pseudomonas

Pseudomonas causes a variety of skin infections. It is the cause of “**hot tub folliculitis**.” Normal chlorine levels may prevent the possibility or growth of infection with this organism. The pustules from hot tub folliculitis are usually around the buttocks and thighs and resolve without treatment in 1 week. Pseudomonal septicemia causes small, dark-centered (necrotic) papules. In a very ill, **neutropenic** patient, this papule can evolve to **ecthyma gangrenosum**—a necrotic ulcer with an erythematous rim (Image 12-21).



Image 12-21: Ecthyma gangrenosum

Animal Bites

S. aureus, *Eikenella*, and *Pasteurella multocida* often cause infection from **dog** and **cat** bites. Human bite infections are caused by multiple bacteria and can cause severe infection.

Treatment: Clean and lavage well and give AM/CL (amoxicillin-clavulanate) as prophylaxis and treatment.

RICKETTSIAL SKIN INFECTIONS

Rocky Mountain spotted fever is usually heralded by several days of fever. Then the patient gets small lesions, which progress in distribution from peripheral to central and in type from **macular** to **petechial** to **purpuric**. As you can see from **Image 12-22**, the skin findings can be deceptively nondescript. See Infectious Disease section, Book 1, for treatment.



Image 12-22: Rocky Mountain spotted fever (medial foot)

SPIROCHETAL SKIN INFECTIONS

The first stage of **Lyme disease** is often associated with erythema migrans (**Image 12-23**). Typically, this is a slowly (over about one week) enlarging, annular erythematous rash with a clear center (looks like a bulls-eye). Occasionally, the center will not be clear.

Syphilis. A chancre (ulcer at site of inoculation) indicates primary syphilis. Diffuse scaling papules on the palms and soles, trunk, penis, and mucosal surfaces suggest secondary syphilis. Gummas occur in tertiary syphilis.

VIRAL SKIN INFECTIONS

Warts (verrucae) are caused by any one of more than 60 types of human papillomaviruses (HPV).

- Verruca vulgaris is the common wart; treat it with liquid nitrogen, topical acids, CO₂ laser, etc.

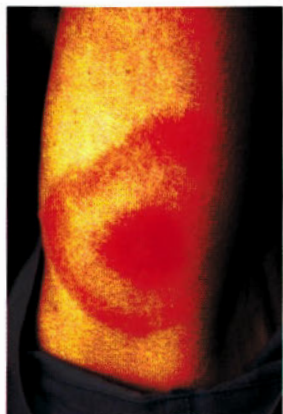


Image 12-23: Erythema migrans

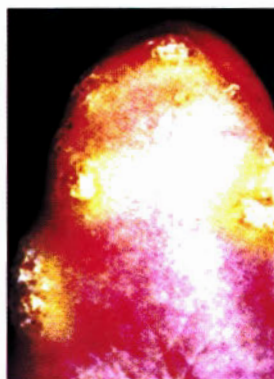


Image 12-24: Plantar wart

- Verruca plana is the flat wart.
- Verruca plantaris is the plantar wart (**Image 12-24**). Initial treatment may consist of a strong acid (trichloroacetic acid), concentrated (40%) salicylic acid plaster, liquid nitrogen, or laser.
- Condylomata acuminata are anogenital warts. They are often caused by HPV 6 and 11. They are sometimes caused by HPV 16, 18, and 31—the oncogenic HPV types (associated with cancer of the cervix). Treat them with podophyllin, trichloroacetic acid, liquid nitrogen, or CO₂ laser. Podophyllin is teratogenic, so do **not** give it to pregnant patients. A newer treatment for condyloma acuminatum is topical imiquimod (Aldara®).

Molluscum contagiosum [Know] is caused by a **pox-virus**. It consists of smooth, umbilicated, pearly papules (**Image 12-25**). It usually occurs in children (anywhere on the body except palms and soles), but you may also see it in the pelvic area of sexually active young adults—and it is common in AIDS patients (can be sexually transmitted).

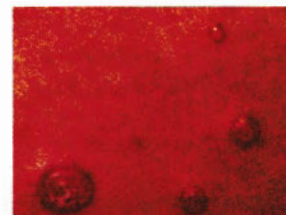


Image 12-25: Molluscum contagiosum

Measles (rubeola; Know) has several stages. The prodromal stage lasts 3–4 days with fever, malaise, sinus discharge, and a hacking cough. Koplik spots often appear on the palate from 1 to several days before the onset of rash. The red maculopapular rash starts on the forehead and quickly spreads downward with the densest concentration of lesions from the forehead to the shoulders.

Rubella (German measles, 3-day measles) is benign except when it occurs in pregnant women. Congenital rubella results in a variety of serious birth defects:

- heart malformations,
- deafness,
- ocular defects,
- TTP, and
- microcephaly,
- bone problems.
- mental retardation,

Varicella-zoster virus (VZV) causes two diseases: chicken pox and herpes zoster (shingles). Both diseases present with vesicles on an erythematous base. Herpes zoster is reactivation of VZV in a person who has had chicken pox.

Chicken pox: Incidence is decreased now due to routine vaccination of children. Rash is initially maculopapular and rapidly progresses to vesicles and then to scabbed lesions. These tend to come in “crops” over 2–4 days.

Herpes zoster (shingles): Grouped vesicles along a dermatome with focal pain. Oral/IV acyclovir helps decrease the length of the disease and the progression to post-herpetic neuralgia. Oral famciclovir and valacyclovir are also effective.

Quick Quiz

- Which antibiotic is used to treat a cat bite?
- Characterize the rash of erythema migrans.
- Molluscum contagiosum, if seen in an adult, should raise your suspicion for what immunodeficiency?
- How does the dose of acyclovir differ when the drug is used to treat varicella and herpes simplex infections?
- What are the treatments for head lice? What topical treatment is not pesticide-based?

In the immunocompromised, you should treat both chicken pox and herpes zoster with intravenous acyclovir at higher doses than what is used to treat herpes simplex infections.

FUNGAL INFECTIONS

Dermatophytes (*Microsporum*, *Epidermophyton*, and *Trichophyton*) cause:

- tinea **capitis** (scalp ringworm),
- tinea **corporis** (common ringworm, [Image 12-26](#)),
- tinea **cruris** (jock itch),
- tinea **unguium/onychomycosis** (nails, [Image 12-27](#)), and
- tinea **pedis** (athlete's foot, [Image 12-28](#)).



Image 12-26: *Tinea corporis*



Image 12-27: *Tinea unguium* or *onychomycosis*

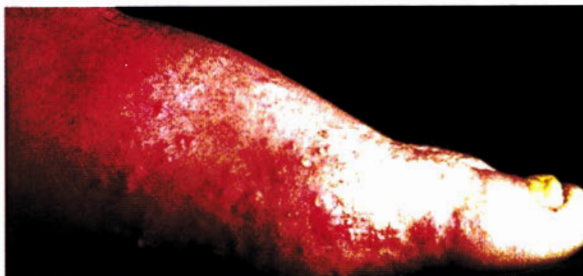


Image 12-28: *Tinea pedis* (athlete's foot)

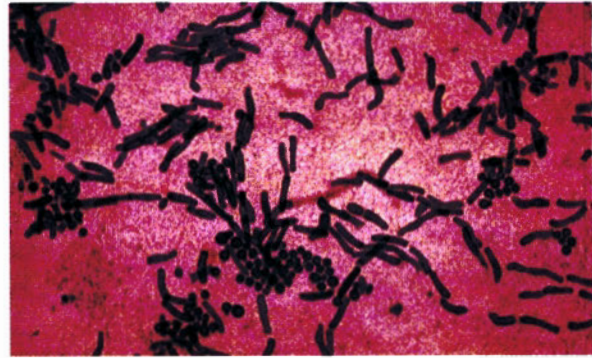


Image 12-29: *Tinea versicolor*

Candidiasis of the mouth (thrush) causes white semi-adherent plaques on the tongue and mucosa. Vaginal candidiasis has similar plaques with cheesy discharge.

Most fungal skin infections are controlled by topical antifungal creams. Miconazole, clotrimazole, and topical terbinafine (Lamisil®) are usually used. Tinea capitis requires **oral** therapy with griseofulvin, terbinafine, or itraconazole. Treat tinea unguium (onychomycosis) with systemic terbinafine, itraconazole, or fluconazole.

Tinea versicolor (pityriasis versicolor) is caused by *Malassezia globosa* or *Malassezia furfur* ([Image 12-29](#)). Skin infection results in hypopigmented or hyperpigmented (depending on the patient's skin tone/color) spreading macules, usually on the upper torso and upper arms. KOH skin scraping: **spaghetti and meatballs**.

Treatment: imidazole creams, selenium sulfide or ketoconazole shampoo, and/or oral itraconazole.

PARASITIC SKIN INFECTIONS

Lice outbreaks usually occur in schools, nursing home communities, and camps.

Head lice (*Pediculus humanus capitis*): The best pesticide-based topical treatment is over-the-counter **permethrin** cream 1% (Nix® cream rinse) because it kills both lice and eggs. It is approved for head lice only. The even more toxic topical medications, 1% lindane shampoo and pyrethrin + piperonyl butoxide (RID®, etc.), do not kill the eggs and require another treatment a week later. In the U.S., **resistance is growing** against **all** common pesticide-based preparations.

A newer treatment that is as effective as RID but contains **no** neurotoxic pesticides is **benzyl alcohol lotion 5%** (Ulesfia®). It kills by suffocating the lice. It is safe in children older than 6 months.

Malathion (topical) is the best prescription **topical** agent. **Ivermectin** (yes, the drug that kills heartworms in dogs; Stromectol®) is the strongest drug; it is given **orally** as 2 doses, 1 week apart. It is considered a 2nd line alternative to malathion.

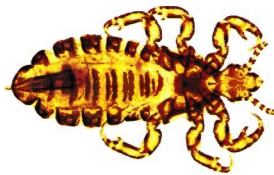


Image 12-30: Body louse

Body lice (*Pediculus humanus corporis*) (Image 12-30) live in clothes and are on the body only when feeding. Treatment is bathing and careful **laundrying** of clothes and bed linens.

1% lindane lotion or pyrethrin + piperonyl butoxide are used if ova and/or parasites are found on the seams of clothing.

Pubic lice (*Phthirus pubis*): The crab louse is sexually transmitted and can also infect the eyelashes. Crab lice are rarely transmitted by fomites. Itching is the most common manifestation of infection. Exam may reveal bluish macules (maculae ceruleae) in the groin area. Treat with topical permethrin or pyrethrin + piperonyl butoxide. Wash bedding and clothing in hot water and use a hot dryer.

Scabies is caused by a mite (*Sarcoptes scabiei*) that tunnels into the skin to lay eggs (Image 12-31). It is spread by skin-to-skin contact—will not live > 48 hours without a host!

Treat with 5% permethrin applied to all areas of the body from the head down and washed off after 8–14 hours, or use oral ivermectin with a repeat dose in 2 weeks. Lindane has CNS toxicity, so do not use it in infants and young children. Precipitated sulfur is considered the safest medication to use in pregnancy.



Image 12-31: Scabies tunnel

SKIN CANCER AND SKIN FINDINGS

Basal cell carcinoma (BCC) arises from epidermal basal cells and is the most common form of skin cancer, especially in Caucasians (Image 12-32). The usual type of BCC is characterized by translucent pearly papules, often with telangiectatic vessels. It spreads by **local extension** and, when large enough, gets a “**rodent-eaten**” appearance.

BCC is caused by ultraviolet (UV) radiation—from sun exposure. It is typically found on sun-exposed areas such as the head and neck, but it may appear elsewhere.

Know that the **meta-static** potential of BCC is < 0.1%.



Image 12-32: Basal cell carcinoma

Squamous cell carcinoma (SCC): From keratinizing epidermal cells, SCC occurs especially in **fair-skinned** persons and on exposed areas, like the dorsum of hands, forearms, ears, and lower lip (Image 12-33). Actinic keratosis can progress to squamous cell carcinoma. In contrast to the low metastatic potential of BCC, SCC has a 0.3–3.7% metastatic potential—and even higher when it appears on the ear (11%) and lower lip (13%)! **Metastatic** rate of recurring tumors is 30%.

Melanoma: This also tends to occur more commonly in fair-skinned people, especially those who had severe sunburn in childhood (Image 12-34). There has been a 300% increase in the past 40 years. Other risk factors are dysplastic nevus (described below), family history of melanoma, a high number of ordinary nevi, a congenital nevus, and immunosuppression. It is almost always completely curable if caught early enough.

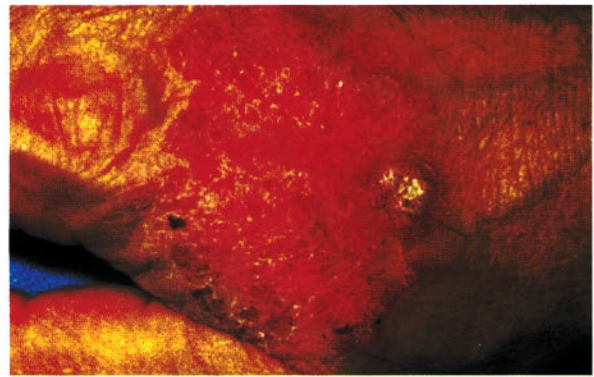


Image 12-33: Squamous cell carcinoma of the hand



Image 12-34: Malignant melanoma—superficial spreading

Quick Quiz

- What is the metastatic potential for basal cell carcinoma?
- On which areas of the body does squamous cell cancer have the highest rate of metastasis?
- For melanoma, what measurement is most important when determining prognosis?
- What are the main forms of cutaneous T-cell lymphoma? Which has the worse prognosis?
- What are the “4 Ds” that patients with glucagonomas develop?
- Characterize the skin findings associated with porphyria cutanea tarda.

Think “ABCDE” when assessing a lesion that might be malignant melanoma:

- Asymmetry
- Borders are irregular
- Colors are variable
- Diameter > 6 mm is suspicious
- Elevated or evolving lesions are more suspicious

Age of the patient, **location** of the lesion, and **(most important) the depth** of the lesion are prognostic factors. Age < 50 and location on the trunk are better prognostic factors.

Lesions < 0.76 mm in depth have a 99% five-year survival; those > 3.6 mm have a < 50% five-year survival.

If the lesion is < 0.76 mm, you may safely excise the melanoma with a 1-cm, tumor-free margin. (Previously, a 5-cm margin was recommended.) Lesions over 0.76 mm in depth should be referred for evaluation for a sentinel lymph node procedure.

Dysplastic nevi are “odd-looking” moles and may even look like melanomas (Image 12-35). They are markers for a propensity to develop malignant melanoma. However, most melanomas arise *de novo* and not in a preexisting nevus. Removing all moles does **not** prevent melanoma development. Standard of care is close follow-up and monitoring, utilizing photographic documentation.

If a patient with a dysplastic nevus has two relatives with malignant melanoma, the patient has a 300x chance of getting malignant melanoma!

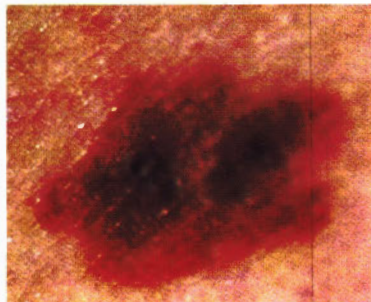


Image 12-35: Dysplastic nevus

Mycosis fungoides and **Sézary syndrome**: These are the main forms of cutaneous T-cell lymphoma. Sézary syndrome has peripheral blood involvement and a poorer prognosis.

Paget disease of the breast is something to consider anytime there is a persistent (despite treatment), unilateral, oozing, eczematous plaque in the area of the areola. It is virtually always due to underlying breast cancer. By far, the **most common** causes of an acute eczema-type rash on an areola are **contact dermatitis** or **skin irritation**. Especially consider Paget disease if there is **no response to treatment**.

Peutz-Jeghers syndrome consists of multiple hamartomatous polyps + melanotic pigmentation (lentigines) on the lips + buccal mucosa. Even though these polyps are hamartomas, there is still **some** risk of cancer because an occasional adenoma will occur. Note that healthy, darkly pigmented people and those with Addison disease may have similar intraoral dark spots.

Glucagonomas (secreting pancreatic alpha-cell tumors) can cause a **beefy red tongue** (think GLucagonoma = GLossitis), angular cheilitis, and a **necrolytic** migratory erythematous rash. Patients with glucagonomas typically develop the “4 Ds”: diabetes, DVT, depression, and dermatitis.

Metastases to the skin: The 4 cancers that most commonly have cutaneous metastases are lung cancer, GI cancer, melanoma, and breast cancer in women.

Macroglossia is associated with pinch purpura, which develops from pinching or stroking the skin; strongly suggests multiple myeloma and/or cutaneous amyloidosis.

BLISTERING LESIONS

Porphyria cutanea tarda (PCT) (Image 12-36, Image 12-37) is the **most common** type of **porphyria**. PCT causes **hyperpigmentation**, **tense blisters** in **sun-exposed** areas, milia, skin fragility, and increased **facial hair**. Porphyria is caused by a congenital or acquired decreased activity of uroporphyrinogen decarboxylase, which allows a buildup of phototoxic porphyrins in the skin. Symptoms



Image 12-36: Porphyria cutanea tarda (PCT)



Image 12-37: Porphyrria cutanea tarda (PCT) with blisters

can be induced by ingestion of estrogen or alcohol! Many patients have associated **hepatitis C**. Lab results usually show an increased serum Fe, Hct, ALT, and AST. To screen, check for increased urinary **coproporphyrins** and **uroporphyrins**. Patients may have dark or pink urine.

Treatment is the same as for hemochromatosis: regular phlebotomies. Antimalarials may also help. PCT due to HCV resolves with treatment of hepatitis.

Porphyria variegata (variegate porphyria) is also known as South African porphyria. Patients may get blisters on sun-exposed areas and have mechanical fragility of the skin. These patients may also have **abdominal pain**, **polyneuropathies**, and **mental disturbances**.

Treatment of acute attacks is the same as for acute intermittent porphyria (AIP): glucose and hematin. Differential diagnosis: Note that AIP presents similarly to variegate porphyria, except without the skin changes. PCT (above) presents with the skin changes and without the neuro/mental changes!

Epidermolysis bullosa: Patients have blistering after minor skin trauma, caused by congenital structural defects of the skin. The skin splits at the junction of the epidermis and the dermis. There are many different classifications. It is genetically transmitted.

Epidermolysis bullosa acquisita, like bullous pemphigoid (next), is also caused by antibodies directed against the basement membrane. The target antigen is type VII collagen.



Image 12-38: Bullous pemphigoid

Bullous pemphigoid causes recurrent crops of **tense** blisters (Image 12-38). Older individuals are usually affected, and the disease process can appear similar to urticaria when it starts. It has an autoimmune etiology with anti-basement membrane antibodies.

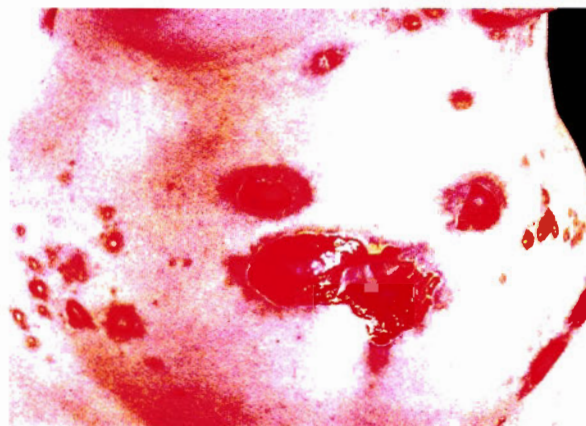


Image 12-39: Pemphigus vulgaris

Pemphigus vulgaris (Image 12-39) is an autoimmune disease with antibodies against the proteins within the epidermis. This causes acantholysis (the separation of epidermal cells from each other due to decreased cohesion), which results in the formation of large, **loose** bullae that peel off and leave denuded skin. Oral mucosal involvement is common, and any cutaneous area can be affected.

Treat pemphigus vulgaris with **high-dose** corticosteroids +/- cyclosporine/azathioprine/cyclophosphamide and IVIG.

Nikolsky sign: Slight lateral pressure on the skin causes sloughing of the epidermis. It is positive in pemphigus vulgaris, toxic epidermal necrolysis (TEN), and staphylococcal scalded skin syndrome (SSSS). It is negative in bullous pemphigoid.

Erythema multiforme consists of well-defined lesions varying from annular to targetoid (Image 12-40). Palms and soles are frequently involved, and mucous membranes may be affected. The targetoid or iris-shaped lesions are pathognomonic for erythema multiforme. The lesions may also be edematous or bullous. It is usually caused by herpes simplex viral infection. *Mycoplasma* and drugs (NSAIDs, penicillins, etc.) can also cause it.



Image 12-40: Erythema multiforme

Quick Quiz

- What type of hepatitis is associated with PCT?
- What is the pathognomonic lesion for erythema multiforme? Which virus often is the cause?
- With what GI disorder is dermatitis herpetiformis associated?
- What is characterized by a “Christmas tree” pattern and a herald patch?

Stevens-Johnson syndrome is a severe form of erythema multiforme, and some authors consider it part of the spectrum of toxic epidermal necrolysis (TEN). Corticosteroids are controversial and should be used for only a very short time, if at all.

Toxic epidermal necrolysis (TEN) is considered a variant of Stevens-Johnson syndrome and is usually caused by a hypersensitivity reaction to a drug (e.g., allopurinol, anticonvulsants, NSAIDs, sulfa, and antibiotics). Like SSSS, it results in a peeling or exfoliation of large areas of skin, but it occurs at a **deeper** level than SSSS. Patients with toxic epidermal necrolysis do poorly (mortality ~40%).

Dermatitis herpetiformis is a skin disease where very pruritic vesicular lesions appear, usually on the extensor surfaces and mid- to lower back, caused by IgA deposition (Image 12-41). Given the extreme pruritus, intact vesicles are often not apparent. It is associated with **celiac disease** (gluten-sensitive enteropathy).

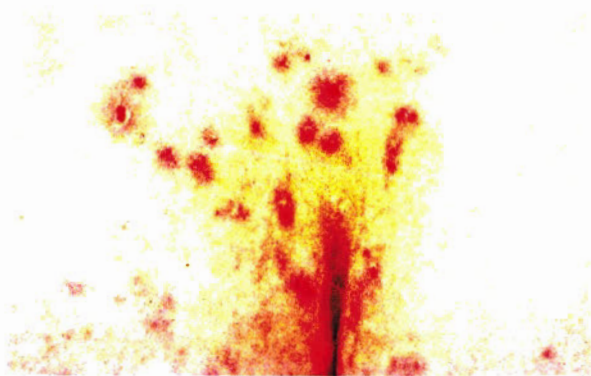


Image 12-41: Dermatitis herpetiformis

ROUND LESIONS

Granuloma annulare is an idiopathic, annular, ring-worm-like lesion without scaling, which usually appears on the distal portion of the extremities (Image 12-42). It often occurs in **children** and **young women**. It usually is **self-limited**, disappearing in months to a few years.

Nummular eczema consists of small, circular (nummular = coin-shaped), pruritic lesions that are more common on the lower legs and are often associated with dry skin and atopy. They are very common in the elderly and have no pathologic significance. Rule out fungal infection. Treat with high-potency topical steroids.

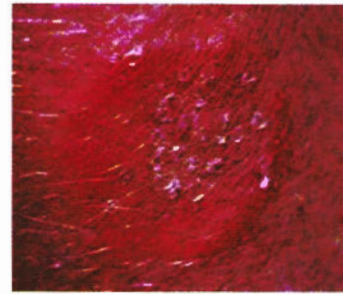


Image 12-42: Granuloma annulare

Pityriasis rosea is a rash you see especially in children and young adults. It probably has a viral etiology (possibly human herpesvirus 6 or 7). The disease is **self-limited**, usually lasting 4–8 weeks.

A **herald patch** precedes subsequent lesions by 1–2 weeks (Image 12-43). This patch is sometimes confused with tinea corporis (Image 12-26 on page 12-11). It develops into small, pruritic papulosquamous oval lesions with the long axis parallel to skin folds and rib lines in a “**Christmas tree**” pattern, usually on the trunk (Image 12-44). Treatment is

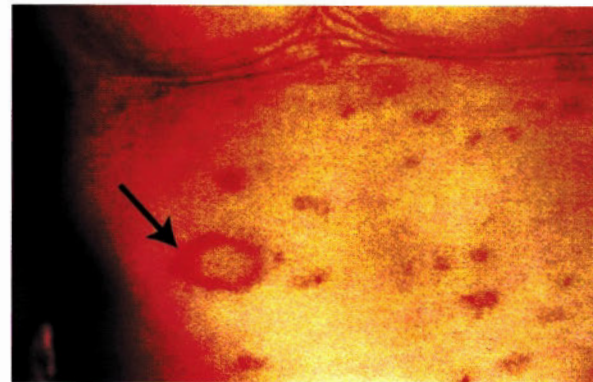


Image 12-43: Herald patch of pityriasis rosea



Image 12-44: Pityriasis rosea; generalized rash

symptomatic. Note: Tinea versicolor (pityriasis versicolor) has **no** relationship with pityriasis rosea.

Urticaria (hives) are **raised pruritic welts** on the skin that can be the manifestation of an allergic reaction. The lesions may have a **smooth or irregular border**. Aspirin is a common cause of urticaria. They can be a manifestation of a connective tissue disease, viral infection, or may be idiopathic. Treatment is primarily with antihistamines.

PIGMENT CHANGES

Vitiligo is an autoimmune, spreading, macular depigmentation (*Image 12-45*). It **usually** occurs in healthy persons, **but, rarely**, it may also be part of the autosomal recessive **polyglandular deficiency**. With this, there may be **any** of the following: DM, Graves disease, Addison disease/adrenal insufficiency, hyper- or hypothyroidism, **hypo**-parathyroidism, and pernicious anemia. Anytime you see a patient with vitiligo, think of these possibilities and screen appropriately!

Tuberous sclerosis is uncommon and autosomal dominant. It is associated with seizures, mental retardation, periungual fibromas, and **hypopigmented (ash-leaf)** macules. You will see these macules best with a Wood's lamp. **Adenoma sebaceum** manifests in these patients as numerous mid-facial papules, which are actually angiofibromas.

Café-au-lait spots are brown macules that occur in association with neurofibromatosis (von Recklinghausen disease) and McCune-Albright disease but also, to a lesser degree, in people with no disease (1–2 spots are normal and common). In neurofibromatosis, 78% of patients have > 6 spots—and 95% have at least one spot > 1.5 cm. In McCune-Albright disease, the spots have a more irregular outline.

Acanthosis nigricans is hyperpigmented skin with a thickened, velvety appearance, noticed mostly in the skin folds (*Image 12-46*). Involvement of the axilla is usually shown as an example. It rarely is familial.

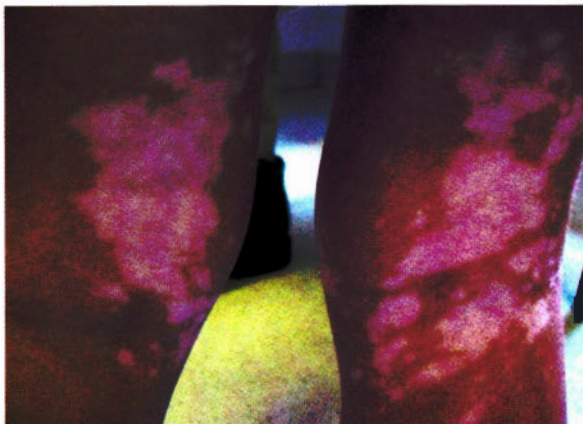


Image 12-45: Vitiligo

Although you will usually see this in **obese** patients, it is also associated with GI cancer, many endocrinopathies, and several autoimmune problems.

The **malignant** acanthosis nigricans is severe and progressive and is usually associated with **gastric adenocarcinoma**.

Associated endocrinopathies include Cushing disease, hyper/hypothyroidism, acromegaly, and diabetes mellitus. Overuse of **niacin** may also cause acanthosis nigricans!

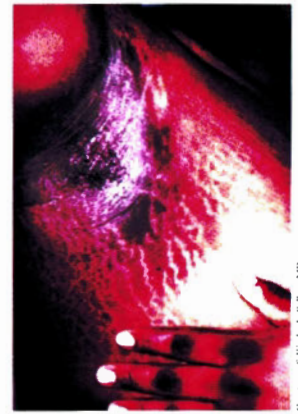


Image 12-46: Acanthosis nigricans

Diffuse hyperpigmentation may occur in primary biliary sclerosis, scleroderma, Addison disease, hemochromatosis (a grayish/bronze coloration), and with the use of the cancer drug busulfan. Other causes include porphyria cutanea tarda, malabsorption and/or Whipple syndrome, pellagra (niacin deficiency), B₁₂ deficiency, and folate deficiency. Check for metastatic melanoma in “slate-blue” patients!

Hyperpigmentation in **sun-exposed** areas can be caused by amiodarone, porphyria cutanea tarda, phenothiazines. Hyperpigmentation is diffuse but darker in sun-exposed areas in pellagra, biliary sclerosis, and scleroderma. Methotrexate can cause a reactivation of sunburn.

Black lesions. Consider the following when you see black lesions:

- Rhinocerebral mucormycosis
- Anthrax
- Ecthyma gangrenosum
- Emboli into distal extremities
- Melanoma/lentigo
- Warfarin skin necrosis

PRURITUS

The most common cause of itching in elderly patients is **dry skin**. Other causes seen across the age spectrum include:

- Hyper- or hypothyroidism
- Malignancy: think lymphoma—especially Hodgkin's, but also breast cancer
- Fe deficiency (even if patient is not anemic)
- Polycythemia rubra vera (aquagenic pruritus)
- Chronic (but not acute) renal failure
- Cholestatic liver disease
- Diabetes mellitus

Quick Quiz

- What skin finding might you see in an autosomal recessive polyglandular deficiency?
- Hyperpigmented areas of the axilla are associated with what underlying disease states?
- What diseases are on the short list of causes of black lesions?
- What is the significance of eruptive xanthomas?

AIDS-RELATED SKIN LESIONS

All skin conditions become more common in HIV/AIDS. AIDS-related lesions include the following: xerosis (dry skin), seborrheic dermatitis (in virtually all patients!), telangiectasias, herpes simplex, herpes zoster, folliculitis, Kaposi sarcoma (KS), and oral candidiasis. Patients with HIV/AIDS can also get condyloma acuminatum (HPV), molluscum contagiosum (poxvirus), and bacillary angiomatosis. Bacillary angiomatosis resembles KS but is caused by a gram-negative bacillus, *Bartonella henselae* (same etiologic agent of cat-scratch disease).

Treat the seborrheic dermatitis with topical low-potency steroids +/- an antifungal shampoo.

The folliculitis is usually due to uncontrolled HIV infection, but it can also be due to a yeast, *Pityrosporum orbiculare*, or *Staphylococcus aureus*. Usually antiretroviral treatment improves these rashes. If no organism is found, consider **eosinophilic folliculitis** (eosinophils seen on biopsy), which can occur in HIV/AIDS.

Oral “hairy” leukoplakia (Image 12-9 on page 12-4) is a **corrugated** tongue with **white** lesions along the **side**. You see it virtually always in patients with HIV infection. Epstein-Barr virus is the cause. It resolves with treatment of HIV.

Kaposi sarcoma is usually seen as < 0.5 cm purple/red/violet macular/papular lesions. They are usually **concentrated** on the **head/neck** and **lower extremities**.

Herpes zoster is often refractory to treatment in patients with HIV/AIDS. Treat with acyclovir or famciclovir. Valacyclovir has been associated with thrombotic thrombocytopenic purpura in the immunocompromised, so it is not recommended.

Disseminated *Cryptococcus* infection may imitate molluscum contagiosum.

DIABETIC SKIN LESIONS

Eruptive xanthomas are due to severe hypertriglyceridemia. They are often seen in diabetic ketoacidosis. They appear abruptly as yellowish-red papules over the extensor surfaces and buttocks. These lesions will resolve when the hyperglycemia is controlled (Image 12-47).

Necrobiosis lipoidica diabetorum can be associated with diabetes in approximately 10–20% of cases (Image 12-48). It is a thin, atrophic, hyperpigmented plaque that appears on the **shins**. It is subject to trauma and ulceration and is thought to be due to microangiopathy.

Diabetic skin spots (diabetic dermopathy) are dark atrophic macules; they are common and often appear on the shins. They have no clinical significance.

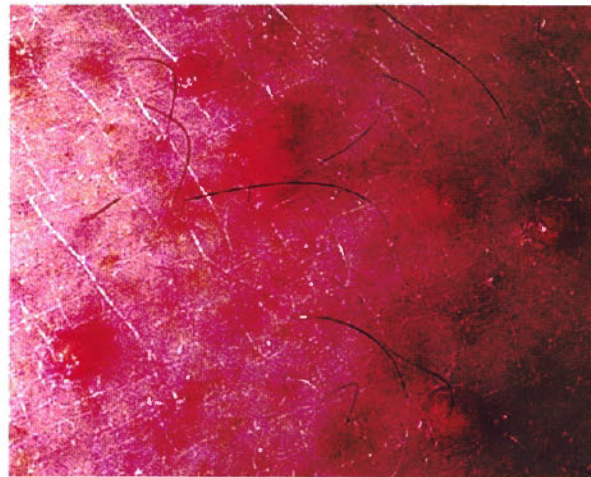


Image 12-47: Eruptive xanthomas in a diabetic



Image 12-48: Necrobiosis lipoidica diabetorum

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